Draft Comparative Effectiveness Review

Number XX

The Role of Immunotherapy in the Treatment of Asthma

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, and health system leaders, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The National Heart Lung and Blood Institute (NHLBI) provided funding for this report.

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new health care technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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The authors gratefully acknowledge the following individuals for their contributions to this project:

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who provided input to this report follows:

Will be included in final report.

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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The Role of Immunotherapy in the Treatment of Asthma

Structured Abstract

Objectives: To evaluate the efficacy and safety of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) in the treatment of allergic asthma.

Data Sources: We searched PubMed, Embase and CENTRAL through June 15, 2016.

Methods: Two reviewers independently screened search results to select randomized controlled trials (RCTs) of the efficacy of SCIT and SLIT, and RCTs, observational studies and case series or case reports that reported on the safety of SCIT and SLIT. For each study, one reviewer extracted the data and a second reviewer verified the accuracy. Two reviewers independently assessed the risk of bias for each study, and together, graded the strength of the evidence for the outcomes of interest.

Results: We identified 47 RCTs on efficacy: 31 assessed SCIT and 16 assessed SLIT. We included 25 RCTs and 16 non-RCTs assessing the safety of SCIT, and 13 RCTs and 8 non-RCTs addressing the safety of SLIT. Heterogeneity and incomplete data precluded meta-analysis.

SCIT reduces the use of long term control medications (moderate strength of evidence (SOE)). SCIT may improve quality of life, reduce the use of quick relief medications (short acting bronchodilators), reduce the need for systemic corticosteroids, and improve FEV_1 (low SOE). There was insufficient evidence regarding the effect of SCIT on asthma symptoms, and on healthcare utilization. Local and systemic reactions were frequent in the SCIT and control groups, but infrequently required a change in dosing (including discontinuation of treatment). For local reactions, calculated risk differences ranged from 32 additional cases of local reactions per 100 people in the placebo group to 40 additional cases per 100 people treated with SCIT. Risk differences for systemic reactions ranged from 0 to 0.319. We are unable to draw conclusions on whether SCIT increased risk of anaphylaxis primarily because the RCTs did not directly measure and report anaphylaxis (insufficient SOE). There was one case report of a death that we determined to be unlikely caused by SCIT.

SLIT improves asthma symptoms (high SOE), improves disease specific quality of life, and decreases use of long term control medication (specifically inhaled corticosteroids) (moderate SOE). SLIT may decrease quick relief medication use and improve FEV_1 (low SOE). There was insufficient evidence to draw conclusions on the effect of SLIT on systemic corticosteroid use, and healthcare utilization. Local (risk differences ranged from -0.03 to 0.765) and systemic reactions (risk differences ranged from -0.03 to 0.06) were a common occurrence in the SLIT and control groups, but infrequently required changes in treatment (including discontinuation of treatment). Life threatening reactions were not commonly reported, with three case reports of anaphylaxis and no deaths reported (insufficient SOE).

There is insufficient evidence about the comparative effects of SCIT versus SLIT, or for differential effects of immunotherapy based on patient age, setting of administration, or type of allergen.

Conclusions: SCIT reduces the need for long term control medication, and may improve asthma specific quality of life, use of quick relief medications, systemic corticosteroids use, and $FEV_{1.}$ SLIT improves asthma symptoms, reduces long term control medication use, improves disease specific quality of life, and may reduce the need for quick relief medication and improve FEV_1. Local and systemic reactions to SCIT and SLIT are common but infrequently required changes in treatment. Life threatening events (such as anaphylaxis) are reported rarely. There is insufficient evidence on the comparative effectiveness of SCIT versus SLIT, or for differential effects in children, by type of allergen, or in clinic versus home setting.

Front Page Box

Purpose of review
To assess the efficacy and safety of immunotherapy for treating allergic asthma

Key messages

- Subcutaneous immunotherapy reduces use of long term control medications (moderate SOE). It may also improve quality of life, $FEV_{1,}$ and reduce the use of quick relief medications (short acting bronchodilators) and systemic corticosteroids (low SOE).
- Sublingual immunotherapy improves asthma symptoms (high SOE), quality of life, and reduces the use of long term control medications (moderate SOE). It may also reduce the use of quick relief medications, and improve FEV_1 (low SOE).
- Local and systemic reactions to subcutaneous immunotherapy and sublingual immunotherapy are common but infrequently required changes in treatment. Life threatening events (such as anaphylaxis) are reported rarely.

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Introduction

Background

Asthma is a chronic inflammatory disorder of the airways, characterized by varying degrees of airflow obstruction. Bronchoconstriction, inflammatory cell infiltration, and airway edema reduce airflow intermittently, often in response to specific exposures, resulting in respiratory symptoms.[1] In the United States (US), the current prevalence of asthma has increased over the past decade, from an estimated 22.2 million Americans in 2005 to 24.0 million Americans in 2014.[2, 3] Asthma can significantly impact patients' and families' quality-of-life and ability to pursue activities such as school, work, and exercise. Globally, asthma ranks 14th based on the burden of disease, as measured by disability adjusted life years.[4]

Asthma affects people of all ages, but it most often starts during childhood. Approximately 62 percent of individuals with asthma also have environmental allergies. Allergic asthma and non-allergic asthma generally have the same symptoms; however, allergic asthma is triggered by inhaling airborne allergens (aeroallergens). An allergen is a typically harmless substance such as house dust mite (HDM), pet dander, pollen or mold. Allergens trigger an IgE-mediated hypersensivity reaction that eventually results in airway inflammation and swelling. In the US, 78 percent of asthmatic children and 75 percent of middle aged adult asthmatics are allergic to one or more inhalant allergens as evidenced by allergy skin testing.[5]

There are currently three treatment options for patients with allergic asthma; allergen avoidance, pharmacotherapy including biologics, and allergen immunotherapy (AIT). Allergen immunotherapy consists of the repeated administration of one or multiple allergens to which the patient is sensitized. AIT offers the advantage of modulating the immune system, reducing IgE-mediated hypersensitivity, and therefore could have long-lasting effects on the control of allergic asthma.

One form of AIT, subcutaneous immunotherapy (SCIT), involves injections of allergen(s) containing solution into the skin. At the beginning of a course of SCIT, the allergen solution is very dilute and becomes more concentrated, increasing the dose of allergen, over time; this "build-up phase" generally takes about 3 to 6 months to complete. When the individual reaches a predetermined therapeutic effective dose or "maintenance dose", the frequency of injections is reduced to every 2-4 weeks, and the dose generally remains the same with each injection during this "maintenance phase". The duration of the build-up phase of SCIT is sometimes shortened by providing injections more frequently in order to reach maintenance more rapidly; this is referred to as "accelerated schedule". With cluster immunotherapy, two or more injections are provided at every visit, usually 1-2 times per week, allowing maintenance doses to be reached in as little as 4 weeks. Rush and ultra-rush schedules are more rapid than cluster immunotherapy, and maintenance can be reached in a few days. Accelerated schedules may carry a higher risk of systemic reactions. Although the optimal duration of SCIT is not well defined, most patients are treated for a duration of 3 to 5 years.[6] Expert recommendations indicate that patients should receive SCIT injections under the supervision of their provider in a facility with the appropriate equipment, medications and personnel to treat anaphylaxis, and be monitored for systemic reactions for 30 minutes.[7]

Other routes of administration for AIT have been assessed, including exposure to the allergen via an aqueous solution or tablet formulation placed under the tongue (sublingual immunotherapy or SLIT) which may be dosed at home. The rationale for this route of therapy is based on its perceived improved

safety margin (reduced risk of anaphylaxis), simple and convenient oral dosing regimen (avoiding the discomfort of injections and the inconvenience of office visits for allergy shots). However, as the dosing of SLIT is done at home, it can be difficult for providers to determine compliance with the treatment.

The 2011 Practice Parameters by the Joint Task Force (comprised of members from the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma and Immunology and the Joint Council on Allergy, Asthma and Immunology) concluded that certain patients with allergic asthma might benefit from SCIT after failure of standard of care.[7] A 2010 Cochrane review concluded, based on moderate quality evidence, that SCIT produced a significant reduction in asthma symptoms and medication in patients with allergic asthma, and an improvement in nonspecific bronchial hyperreactivity as measured by response to methacholine or acetylcholine challenge tests.[8] A 2015 Cochrane review found there was low quality evidence that SLIT reduces inhaled corticosteroid use, and very low quality evidence regarding bronchial provocation, in patients that included those with asthma with rhinitis and other associated conditions.[9] In 2013, the Johns Hopkins University Evidence-based Practice Center (JHU EPC) completed a review of AIT for the treatment of allergic rhinoconjunctivitis and/or asthma.[10] The evidence report found high strength of evidence that SCIT reduces asthma symptoms and medication use, and that SLIT in the aqueous form reduces asthma symptoms.

In 2007, the Expert Panel Report (EPR-3) from The National Heart, Lung and Blood Institute (NHBLI)[1] included SCIT as a therapy to be considered in cases of mild to moderate persistent asthma. In 2015, a working group was convened to select the most relevant topics for systematic review to update the EPR-3. This systematic review focuses on one of those high priority topics, expanding the scope of the prior evidence report to assess the efficacy and safety of SCIT and SLIT, in aqueous and tablet forms, in people with allergic asthma.

Key Questions

Key Question 1: What is the evidence for the efficacy of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

a. Does this vary among subpopulations of interest?
b. Does this vary by setting?
    i. Clinic
    ii. Home

Key Question 2: What is the evidence for the safety of SCIT in the treatment of asthma?

a. Does this vary among subpopulations of interest?
b. Does this vary by setting?
    i. Clinic
    ii. Home

Key Question 3: What is the evidence for the efficacy of sublingual immunotherapy (SLIT), in tablet and aqueous form, for the treatment of asthma?

a. Does this vary among subpopulations of interest?
b. Does this vary by setting?
    i. Clinic
    ii. Home

Key Question 4: What is the evidence for the safety of SLIT, in tablet and aqueous form, for the treatment of asthma?

a. Does this vary among subpopulations of interest?
b. Does this vary by setting?
    i. Clinic
    ii. Home

Figure 1. Analytic framework

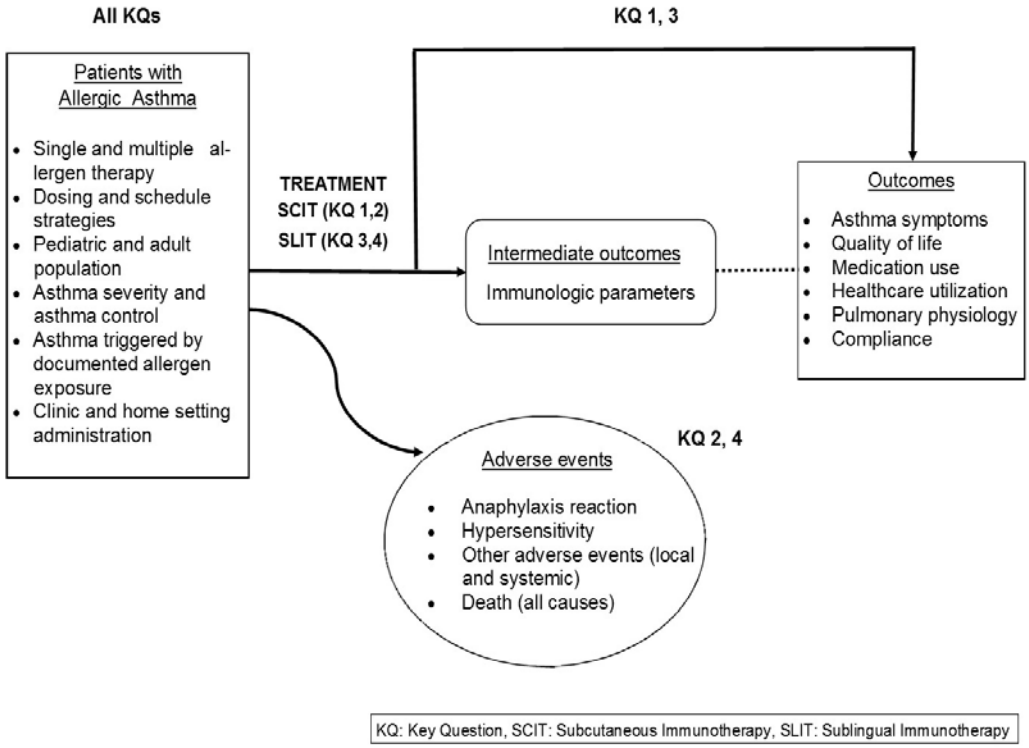


Figure 1. This figure depicts the key questions (KQs). The figure illustrates how immunotherapy administered to patients with allergic asthma may effect intermediate outcomes such as changes in immunologic parameters and/or outcomes such as symptoms, quality of life and medication use. In addition, adverse events may occur at any point after treatment is received.

Methods

Protocol

We recruited a Technical Expert Panel that provided input during the development of the protocol. Protocol development was conducted with guidance from our Task Order Officer (TOO) from the Agency for Health Care Research and Quality (AHRQ) and representatives from the National Heart, Lung and Blood Institute (NHLBI).

The protocol was registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO) registration number CRD42016047749, and posted on the AHRQ website (http://www.effectivehealthcare.ahrq.gov/)

Search Strategy

We searched PubMed, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) from 2005 through June 15, 2016 (see Appendix B for detailed search strategy). (The search is being updated during review of draft report.) Scientific Information Packages (SIPs) were requested from industry representatives, and no information was provided. We also hand searched prior reviews and guidelines,[7, 8, 11, 12] searched ClinicalTrials.gov, and reviewed the FDA Adverse Event Reporting System (FAERS). We will update the search while the draft report is posted for peer review.

We uploaded the search results into DistillerSR (Evidence Partners, Ottawa, Ontario, Canada), a Web-based service for systematic review and data management. We used this database to track the search results at the levels of abstract and full-text screening, and for data abstraction.

Study Selection

We followed the PICOTS (Table 1) framework in developing the criteria for inclusion of studies. We included studies of patients of any ages with diagnosis of allergic asthma. We included studies of patients with asthma, and studies of asthma and other allergic conditions, when outcomes were reported separately for the subgroup with asthma. Studies had to report on the outcomes pre-specified on our PICOTS and had to have an intervention arm receiving either SCIT or SLIT (aqueous or tablet). We excluded studies on food allergies or aeroallergens not related to asthma or if the type of allergen was not specified. Study inclusion was not restricted by language of publication or treatment duration. We included only RCTs for the key questions on efficacy (KQ 1 and 3). We included RCTs, observational studies, case series and case reports for the key questions on safety to be inclusive as possible of any safety concerns (KQ2 and 4). We also re-evaluated all of the included studies in the 2013 systematic review[10] to confirm eligibility for this review.

Abstracts and full-text articles were screened independently by two reviewers. Any disagreements regarding inclusion were resolved through discussion, and unresolved conflicts were adjudicated during team meetings.

Table 1. PICOTS (populations, interventions, comparisons, outcomes, timing, and setting) criteria for including studies in the review.

Populations	• Patients of any ages with allergic asthma • Patients with diagnosis of asthma and positive allergy testing based on allergen specific IgE sensitization diagnosis: Serologic multiallergen screen IgE tests (skin prick tests, serum tests, or both) • Patients with all severity grades and control status of asthma (based on the EPR-3 classification) • Subgroups o Single versus multiple allergen o Pediatric (younger than 12 years of age) and adult population (12 years and older)
Interventions	• Subcutaneous Immunotherapy • Sublingual Immunotherapy (tablet or aqueous)
Comparators	Immunotherapy versus • Placebo • Pharmacotherapy (Usual care) • Immunotherapy
Outcomes	**Outcomes for Key Questions 1 and 3** • Asthma symptoms/outcomes o Asthma control composite scores ▪ Asthma Control Test (ACT) ▪ Asthma Control Questionnaire (ACQ) ▪ Pediatric Asthma Control Test (P-ACT) • Quality of Life o Asthma-specific quality of life- Asthma Quality of Life Questionnaire (AQLQ) o Pediatric Asthma-specific quality of life- Asthma Quality of Life Questionnaire (PAQLQ) o School/Work absences • Medication use o Asthma specific medication use (name, dose, duration) o Long term control medication use o Quick relief medication use (short acting bronchodilators) o Systemic corticosteroids for asthma • Asthma exacerbations / Healthcare utilization o Asthma-specific hospitalizations o Asthma-specific Emergency Department (ED) visits (separate urgent care visits when they can be differentiated) o Asthma-specific ICU admission/intubations o Asthma-specific outpatient visits o Resource use related to the intervention (personnel time and equipment) • Pulmonary physiology: o Spirometry: Peak expiratory flow (PEF), forced expiratory volume (FEV), forced vital capacity (FVC), forced expiratory flow (FEF) as absolute, percent predicted and important ratios (FEV1/FVC) that reflect airway flow. • Airway hyperresponsiveness (AHR) (Methacholine challenge, allergen challenge and exercise challenge) • Compliance with immunotherapy <u>Intermediate outcomes (KQ1 and KQ3)</u> • Immunologic parameters o Allergy skin testing o Allergen-specific Immunoglobulin E (IgE) o Allergen-specific Immunoglobulin G4 (IgG4) **Outcomes for Key Questions 2 and 4** • Anaphylaxis reaction • Hypersensitivity reaction • Other adverse effects of immunotherapy (local and systemic effects) • Death (all-cause, asthma related)
Timing	Studies with all lengths of follow-up duration considered
Setting	Home or Clinic

Risk of Bias Assessment

Two reviewers independently assessed each study's risk of bias using a tool specific to the study design. We resolved disagreements through discussion or adjudication by a third reviewer, as needed.

Randomized Controlled Trials. We assessed the risk of bias of RCTs using the Cochrane Collaboration's tool according to the guidelines in Chapter 8 of the C*ochrane Handbook for Systematic Reviews of Interventions*[13] The following domains were assessed for each RCT:

- Allocation sequence generation
- Allocation concealment
- Blinding of participants and investigators
- Blinding of outcome assessors
- Incomplete outcome data adequately addressed
- Selective outcome reporting
- Other potential threats to validity

Each criterion was reported as "Yes" (low risk of bias), "No" (high risk of bias), or "Unclear" (information is insufficient to assess). Overall risk of bias was graded as Low, Moderate or High.

We did not re-assess each risk of bias domain for the RCTs from our prior review. However, we re-assessed the overall risk of bias for each study to be consistent with the methodology of this review.

Observational Studies. We used the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) tool to assess the methodological quality of non-randomized studies included.[14](See Appendix C for abstraction and instruction forms). We evaluated:

- Selection bias; Sequence generation and allocation concealment.
- Detection bias; Masking of participants, study investigators, outcome assessors.
- Attrition bias; Incomplete outcome data.
- Reporting bias; Selective outcome reporting.
- Other sources of bias.

Each criterion was reported as "Low", "Moderate", "Serious", "Critical" or "no-info". Overall risk of bias was graded as Low, Medium or High, following guidelines.

Case Reports and Case Series. We used the World Health Organization (WHO) criteria to judge the likelihood that the intervention was causally related (dose and time related) to the observed serious adverse event.[15] Following this guidance, we report causality as Certain/Probable, Likely/Possible, Unlikely/Conditional, Unclassified/Unassessible or Unclassifiable.

Data Synthesis

We completed a qualitative synthesis for all questions. Before conducting meta-analyses, we discussed the minimum characteristics required to identify studies sufficiently homogenous to analyze together, such as variability in patient characteristics, allergen and dose used, study duration and outcome definitions. If we had two or more studies similar enough to pool, we would have performed a random-effects meta-analysis using the Hartung-Knapp method[16] with Stata version 14.0 (StataCorp LP, College Station, TX).

To select studies for our preplanned subgroup analysis based on age, we classified studies as pediatric (under age 12) or adult (12 years or older). Studies that did not provide separate results for each population were classified as mixed age population. (In some of these studies, the population age clearly included both categories and ages crossed the 12 year-old cutoff, in some studies, authors did not

provide enough data, age ranges cross the cutoff or authors provided only means or medians without standard deviations.)

To perform our preplanned subgroup analysis based on allergen, we classified studies as single and multiple allergen, and within the single allergen group we grouped studies based on specific allergens (HDM, grasses, weeds, molds, animals).

We did not prepare any funnel plots to assess reporting bias, because due to high heterogeneity, we could not pool more than 10 studies for any outcome analyzed.

Strength of the Body of Evidence

We graded the strength of evidence on the most critical outcomes, as specified in the protocol: asthma control composite scores, healthcare utilization (asthma specific hospitalizations, asthma-specific ED visits (asthma specific ICU admission/intubations) and asthma specific outpatient visits), asthma-specific detailed medication use (quick relief medications, long term control medications, systemic corticosteroids), spirometry (FEV_1 percent predicted), quality of life, anaphylaxis and death. We used the grading scheme recommended in the EPC Methods Guide[17] and updated by Berkman and colleagues.[18] We considered all domains when grading the strength of evidence for an outcome: study limitations (called risk of bias in this review), directness, consistency, precision, and reporting bias.[17] We classified the strength of evidence (SOE) for each critical outcome into four category grades: high, moderate, low, and insufficient. RCT and non-RCT evidence was graded; we did not grade case reports/case series.

Applicability

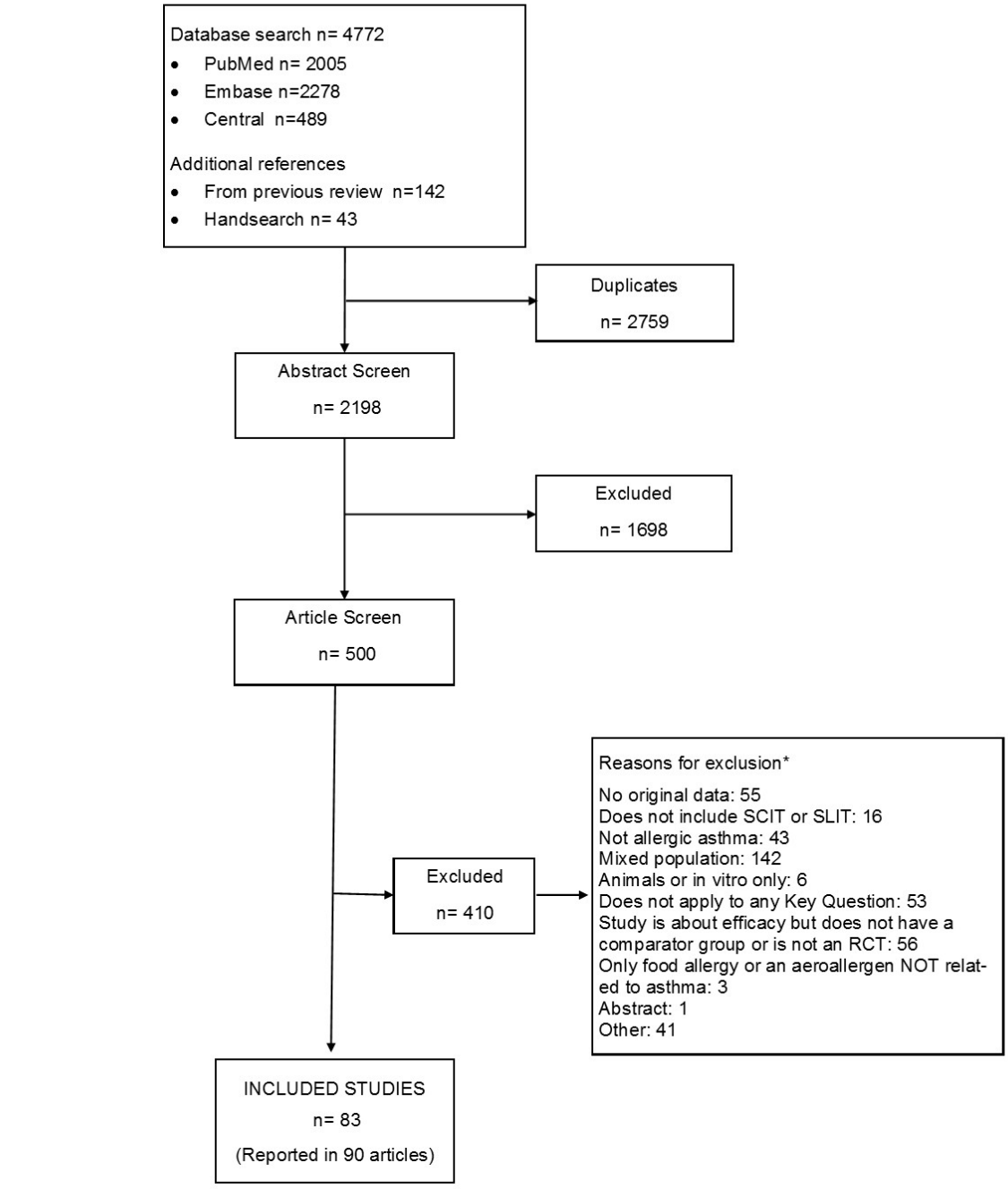
We considered elements of the PICOTS framework when evaluating the applicability of evidence to answer our Key Question as recommended in the Methods Guide.[17] We considered important patient characteristics, differences in severity of asthma and types of allergens, and intervention characteristics that may cause heterogeneity of treatment effects and limit applicability of the findings. We also considered the use of validated tools and heterogeneity of outcomes definitions.

Results

Results of the Search

The search identified 2198 citations and we included 142 from the previous review. We excluded 1698 during abstract screening. During article screening, we excluded an additional 410 articles (see Appendix D, List of excluded articles) that did not meet one or more of the inclusion criteria. We included 61 RCTs (68 articles) and 22 non-RCTs. (Figure 2.)

Figure 2. Search Flow diagram



*Total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.
Other reasons for exclusion: No outcomes of interest, Type of allergen or immunotherapy not specified, pooled data, data not abstractable.

Overall Study Characteristics

We identified 31 RCTs (35 articles) that addressed the efficacy of SCIT (KQ1), 26 RCTs (29 articles) and 15 non-RCTs that addressed the safety of SCIT (KQ2), 16 RCTs (18 articles) that addressed the efficacy of SLIT (KQ3), and 13 RCTs (15 articles) and eight non-RCTs that addressed the safety of SLIT (KQ4). We included 41 studies including adults only (older than 12 years of age), 31 with mixed age population (studies that included adults and children, and that did not provide separate results for each population) and 11 that included only children (younger than 12 years). We provide details of studies identified per age group on Figure 3.

Thirty-four studies compared immunotherapy versus placebo, twelve studies compared immunotherapy versus pharmacotherapy, eleven studies compared immunotherapy versus immunotherapy (one compared three versus five years' treatment[19] and one compared children versus adults[20]), one study compared SCIT versus a desensitization vaccine (the control group received standardized glucocorticoid management and a desensitization vaccine, details not provided), 20 studies did not have a comparator and six studies compared SCIT versus SLIT.

Table 2. Number of studies Included per Key Question, study design, age group and setting

		KQ1 SCIT Efficacy	KQ2 SCIT Safety (RCT/Non-RCT)	KQ3 SLIT Efficacy	KQ4 SLIT Safety (RCT/Non RCT)	SCIT vs SLIT	TOTAL
Study Design	**RCTs**	31	26	16	13	5	58
	Non RCTs	0	16	0	8	1	25
Age Group	**Adult**	13	19 (12/7)	10	20 (8/4)	3	41
	Mixed	15	19 (10/9)	3	6 (4/2)	1	31
	Children	3	4 (4/0)	3	3 (1/2)	2	11
Setting	**Clinic**	28	36 (24/12)	2	6 (4/2)	5	48
	Home	0	0	4	6 (2/4)	0	8
	Not Specified	3	6 (2/4)	10	7 (5/2)	0	23
	Both	0	0	0	2	1	3
	TOTAL	**31**	**42**	**16**	**21**	**6**	**83**

All RCTs required patients to have positive allergy skin testing (SPT) and/or in vitro specific IgE testing, however criteria varied widely within studies (wheal diameter within 3 and 7 mm and IgE values varied in values and units) and some studies did not describe criteria for what was considered a positive test. Allergy diagnosis criteria was not reported in eight of the non-RCTs included for safety on SCIT.[21-27]

No consistent criteria were applied to establish asthma diagnosis (the criteria were not described in 34 studies, GINA criteria were used in 28 studies, and the remaining studies used clinical criteria, pulmonary function testing or other definitions). We found no consistency in how asthma severity or level of asthma control was defined among studies.

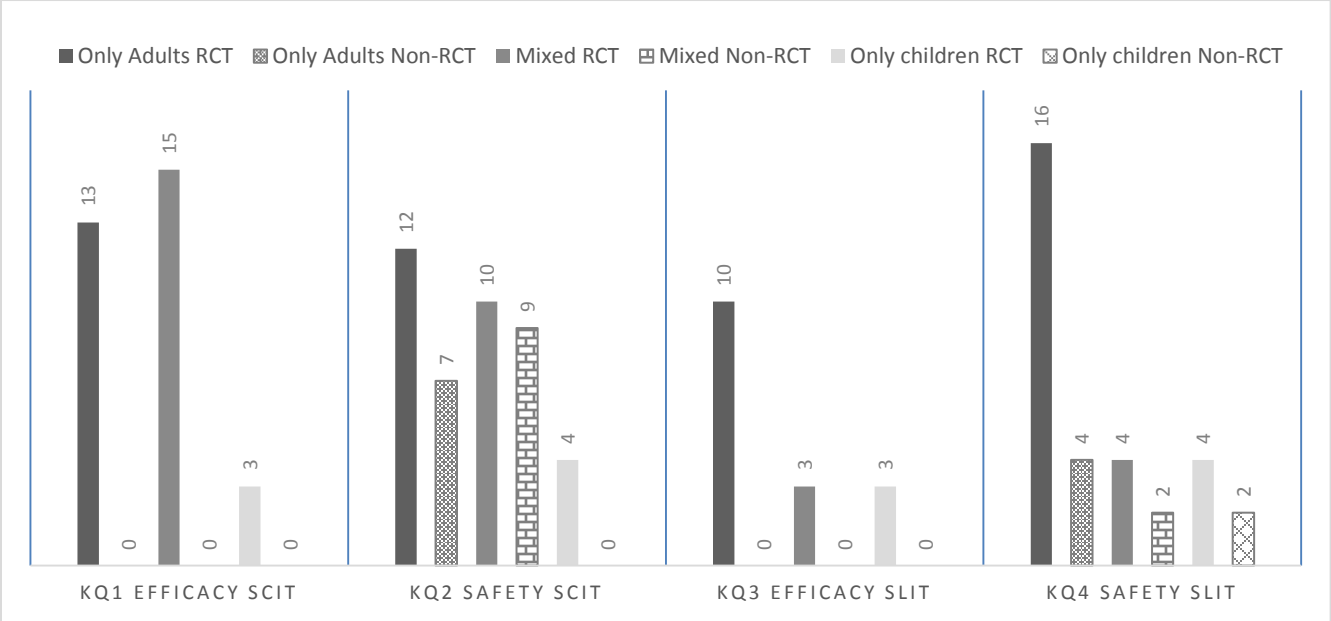
Patients were monosensitized in 41 studies (23 on SCIT, 14 on SLIT and four on SLIT vs SCIT) and polysensitized in 14 studies (seven on SCIT, six on SLIT and one on SLIT vs SCIT). Nine studies (four on SCIT and five on SLIT) included both polysensitized and monosensitized patients, eight studies (seven on SCIT and one on SLIT) did not report the results of the allergy diagnosis and/or allergen identified and 12 studies (nine on SCIT, two on SLIT and one on SLIT vs SCIT) did not clearly report sensitization status (patients were specifically sensitive to one allergen but authors did not specify sensitization status to other allergens). (See definitions in Appendix B.)

Patients received single allergen immunotherapy in 69 studies (55 RCTs and 14 non-RCTS) and multiple allergen immunotherapy in 14 studies (3 RCTs and 11 non-RCTs).

House dust mite (HDM) was the most common allergen used, with 47 HDM studies (DPter, Dfar, DPter-Dfar combined, or unspecified HDM). All the other allergens were used much less frequently; 14 studies used multiple allergen, eleven used grass, five used trees (four on birch and one on cypress), two used mold (alternaria and cladosporium), three on animal allergens (two on cat and one dog) and one ragweed.

Details of study and patient characteristics are provided in Tables 1 and 2, Appendices E, F, G and H.

Figure 3. Number of Included Studies per Key Question and Age Group



Key Question 1. What is the evidence for the efficacy of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

Key Points

- SCIT reduces the need for long term control medication (moderate SOE).
- SCIT may improve asthma specific quality of life, decrease use of quick relief medications, decrease use of systemic corticosteroids and improve FEV_1 (low SOE).
- There was insufficient evidence regarding effect of SCIT on asthma symptom control and healthcare utilization.
- There was insufficient evidence about any differential effect of SCIT in pediatric patients.

Overall Study Characteristics

We identified 31 RCTs (35 articles) that addressed the efficacy of SCIT. Thirteen RCTs (15 articles) included adults, 15 RCTs (17 articles) included a mixed age population and 3 studies included only children. Eighteen studies compared SCIT versus placebo, nine studies compared SCIT versus pharmacotherapy, three studies compared SCIT versus SCIT (one compared three versus five years'

treatment) and one study compared SCIT versus a desensitization vaccine (standardized glucocorticoid management and a desensitization vaccine, details not provided).

Patients were monosensitized in 17 studies and polysensitized in five studies.[28-32] Two studies included both polysensitized and monosensitized patients,[19, 33] and seven studies did not clearly report sensitization status.[34-40] Patients received single allergen immunotherapy in 28 studies and multiple allergen immunotherapy in 3 studies.[28, 31, 32]

HDM was the most common allergen used, with 20 HDM studies. All the other allergens were used much less commonly; three studies used multiple allergen, two used cat, two grass, two used mold (alternaria and cladosporium), one ragweed and one dog.

Details on study, patient characteristics, and interventions are provided in Appendix D and components in the assessment of risk of bias are shown in Appendix I.

Asthma Symptoms

No studies reported on asthma symptom control using ACT, ACQ or P-ACT scores.

Quality of Life

Four studies, three with HDM allergen and one with alternaria allergen, with a total of 194 patients, examined the impact of SCIT on disease specific quality of life using the Asthma Quality of Life Questionnaire (AQLQ).[41-44] Two studies included only adults, and two were studies with mixed ages. We assessed three studies as having moderate risk of bias, and one study as high risk of bias (based on lack of allocation concealment and blinding).

Two studies showed statistically significant differences in quality of life compared to control [43, 44] while two showed differences that were not significant.[41, 42] The two studies with significant improvement in quality of life included only adults with mild and moderate persistent asthma, treated with HDM allergen for 54 and 55 weeks.[43, 44] The differences in overall AQLQ from these two studies were approximately 4 points (P=0.043) and 6 points (P=0.0025), respectively. The studies that did not show statistically significant improvements in AQLQ were in mixed age populations with mild or moderate persistent asthma, treated with either alternaria allergen for 12 months or HDM allergen for 8 months.[41, 42]

Overall, SCIT may improve quality of life as measured by the AQLQ (low SOE, with consistent but imprecise results and medium risk of bias).

No studies reported asthma specific quality of life using Pediatric Asthma Specific Quality of Life Questionnaire (PAQLQ) or school or work absences.

Medication Use

We identified six studies that reported on medication use.[40, 42, 43, 45-48]

Quick relief medications. One study of adults receiving HDM SCIT reported a decrease in the use of quick relief medication (short acting beta agonists; SABAs). The study reported a statistically significant reduction in medication use among those receiving SCIT (decrease from 27 to 14 puffs/week, P<0.05), and a non-significant reduction in the control group (decrease from 52 to 46 puffs/week, P NS).[45] There was a substantial change but the duration of treatment was not clear from the study report. Overall, SOE was low for the effect of SCIT on quick relief medication use, based on one small study (n=31) with low risk of bias.

Long term control medications. We identified five studies that reported changes in use of long term control medications, including two in adult populations [48, 50] and three in mixed age populations.[40, 42, 43, 45, 46] All of these studies reported use of inhaled corticosteroids, though the metrics varied (e.g., dose in micrograms, rates of discontinuation, or number of weeks free of use). The approach to adjustment of ICS varied across studies and did not appear to follow strict protocols for dosage adjustment. One of these studies also compared a variety of regimens including leukotriene receptor antagonists (LTRA) and long acting beta agonists (LABA) in addition to use of inhaled corticosteroids.[42] Overall risk of bias was low in two studies, moderate in two and high in one, the latter with issues of allocation concealment and blinding. The five studies included 283 patients and all were studies of HDM allergen. Treatment ranged from 8 months to 54 weeks.

One study of adults with mild to moderate persistent asthma showed a statistically significant increase in weeks free from inhaled corticosteroids use in the SCIT group when compared to placebo (P<0.001).[43] Similarly, another study that compared SCIT alone and SCIT with co-administration of Vitamin D, the SCIT groups (analyzed together) had a higher rate of inhaled corticosteroids discontinuation compared to the control group (28 versus 0 %, P=0.002).[40] One study reported a significant reduction in inhaled corticosteroids dose in the SCIT group during the study (38%, P <0.05) and a non-significant change in the control group,[45] while another showed a significantly greater reduction in inhaled corticosteroids dose in SCIT versus control after 3 years of treatment (P=0.027).[46] In the latter study, the control group received treatment with a desensitization vaccine (standardized glucocorticoid management and a desensitization vaccine, details not provided). Finally, in the study that assessed use of multiple long term control regimens (including inhaled corticosteroids, LTRA, and LABA) there was a significant reduction in need for any long term control medication in the SCIT group (decrease from 17 to 8 of 21) (P<0.046), but not in the control group (increase from 11 to 13 of 20) (P=0.158).[42]

Overall there was moderate strength of evidence that SCIT reduces use of long term control medications, based on consistent and precise evidence, with medium risk of bias.

Systemic corticosteroids. Two studies of SCIT, including 150 patients, reported change in systemic corticosteroid use.[31, 47] The studies included a mixed age population treated with HDM allergen for three years and a pediatrics study of treatment with multiple allergens for 27 months. Asthma severity was not reported in either study, but the pediatric study included children with controlled asthma. In the mixed age study, there was a significantly greater reduction in annual days of systemic corticosteroid use in the SCIT group (decrease from 22 to 1 day per year) compared to the controls (decrease from 25 to 12 days per year), (SCIT versus control, P<0.01).[47] In the pediatric study, there was no significant difference in systemic corticosteroid use in SCIT versus control (-1.9 vs. -1.7 days in past 60 days, P=0.49) [31] Overall there was low SOE that SCIT reduces use of systemic corticosteroids given the inconsistent results in the two studies.

Asthma Exacerbations

Two studies of SCIT reported asthma exacerbations.[30, 47] The studies, enrolling 95 patients, treated mixed age populations with HDM allergen for either two or three years. One study included patients with well controlled asthma,[30] and in the other study, asthma severity and control status were not reported.[47] In the study that treated for 3 years there was a statistically significantly greater reduction in risk of asthma exacerbations in the SCIT group (decrease from 8+/-1.8 to 1+/-0.5 per year) compared with controls (decrease from 8.5 +/- 1.7 to 4.25 +/- 0.25 per year) (SCIT vs. control, P <0.01).[47] In the

other study, exacerbation rates were low for each group (two in the SCIT group and one in the control), but there were no reported comparisons between groups.[30]

Healthcare Utilization

Two RCTs in children reported on healthcare utilization.[31, 49] One RCT evaluated HDM SCIT compared with pharmacotherapy alone for six months in 40 children, and found that patients in the SCIT arm had a significantly higher number of clinic visits in six months compared with controls, but the number of emergency room visits and hospitalizations were not significantly different between arms.[49] The authors do not provide an explanation for the significant increase in clinic visits in the SCIT arm. The second RCT enrolled 121 children and compared multiple allergen SCIT versus placebo for 30 months. [31] This RCT reported no difference in the number of office visits, ED visits, or hospitalizations between baseline and final follow up for either arm and there were no differences between groups for any outcome. Two small RCTs with medium risk of bias found the following: inconsistent and imprecise results for clinic visits; and consistent but imprecise findings that there was no significant change in hospitalizations or emergency department visits. Overall the strength of evidence is insufficient.

Pulmonary Physiology

PEF. Nine studies of SCIT reported peak expiratory flow rate (PEF) as an outcome, including 664 patients.[30, 31, 34, 41, 46, 50-53] Most of these studies enrolled mixed age populations, and two enrolled adults only.[34, 53] Most of these studies (5 of 9) employed HDM allergen. Two studies were of mold allergens (cladosporium and alternaria), one was of ragweed allergen, and one was of mixed allergens. Peak flow values were reported in the studies as a mean daily, morning, and/or evening value. Treatment ranged from 6 months to 2 years. Overall risk of bias was low in four studies, moderate in four and high in one, the latter with issues of allocation concealment and blinding.

Seven of nine studies reported statistically significantly improved PEF with SCIT compared with controls.[30, 31, 34, 41, 46, 50, 53] In one study of HDM allergen,[51] there was a significant increase in PEF in the SCIT group during the study, but the change was not significantly different when compared to the change in the control group. This study enrolled patients with mild to moderate persistent asthma and treated for one year. In the study of cladosporium allergen, there was not a significant difference in PEF between the SCIT and control groups.[52] This study enrolled patients with mild and moderate persistent asthma and treated for 10 months.

Both studies in adults showed significant improvement in PEF. In one study of HDM allergen in only adults,[34] morning PEF improved significantly in the SCIT group but not the controls. In this study, treatment was for 6 months and the asthma patients were controlled at baseline. In the other study of adults, ragweed allergen was used and there was a statistically significant difference in PEF between SCIT and control, when measured in the morning during the peak allergen season.[53]

FEV_1. There were six studies of SCIT, including 548 patients, that reported FEV_1 as an outcome,[32, 41, 42, 51, 54, 55] including one of the studies that also reported PEF as an outcome.[51] Four studies were of HDM allergen, one of alternaria, and one of multiple allergens. In one study, there was a significantly greater increase in FEV_1 percent predicted in SCIT versus control (change from 82 to 99 percent predicted versus 86 to 83 percent predicted, P <0.001).[55] In this study, patients were treated with 7 weeks of therapy with HDM allergen. Asthma severity and control at baseline were not reported. In another study, FEV_1 improved in the SCIT group (73 to 96 percent predicted, P =0.008), but the change was not compared to the change on the control group.[41] This study used alternaria allergen in patients with mild and moderate persistent asthma for 12 months. In one of the pediatric studies, the authors reported the

number of patients with improvement in the study groups, with a significantly greater number improved in SCIT compared to control (P=0.0001).[32]

In the study that also reported significantly improved PEF,[51] there was not a corresponding increase in FEV_1. Another study reported significant changes in FEV_1within the SCIT arm (P<0.001) but not for the placebo arm (P>0.05), without providing direct comparison between the groups.[54] Another simply reported that at 8 months all patients had FEV_1 > 80 percent predicted, but did not report changes from baseline.[42]

Overall, there was low SOE that SCIT improves FEV_1; the findings were consistent and precise, but risk of bias was high.

FEV_1/FVC. No study of SCIT reported FEV_1/FVC as an outcome.

FVC. One study reported change in FVC.[51] This study randomized 132 patients with mild to moderate asthma and treated with dust mite allergen for one year. There was no statistically significant increase in FVC in either the SCIT or placebo groups..

Airway Hyperresponsiveness (AHR)

Methacholine challenge. Seven studies reported methacholine challenges results, with two HDM studies in adults,[47, 50] two HDM studies in mixed populations,[30, 56] one alternaria study in mixed age population,[41] one of cat allergen in adults[35] and one of multiple allergen in children.[31] The studies included 388 patients. Overall, two studies showed improvement in AHR, while five did not.

The study of alternaria did show significant improvement in AHR when compared to pharmacotherapy (P=0.03).[41] In this study, monosensitized patients with mild and moderate persistent asthma were treated for 12 months.

In the four studies of HDM allergen, one showed significant improvement in AHR, while three did not show an improvement. In the study showing improvement in AHR, patients in the SCIT group had a significant increase in PD20 compared to control group, after 3 years of treatment. Disease severity was not reported.[47] In the three studies that did not show improvement, asthma status of enrollees was mild to moderate severity, well controlled, and not specified, with treatment durations of three years, two years and seven months, respectively.[30, 50, 56] Neither the study of cat allergen[35] or multiple allergens[31] showed improvement in AHR (Appendix D - Table 10 for details).

Allergen challenge. There were 13 studies that reported results of allergen challenges, including eight with HDM, two cat, and one each for dog, cladosporium and ragweed. Nine studies were done in adults (N=369),[34-36, 43-45, 53, 55, 56] and four included mixed populations (N=110).[29, 37, 38, 52]

Overall, most (nine of 13) studies showed statistically significant improvement in AHR with SCIT compared with the control group and one study showed significant improvement in the SCIT group, but not in the control group.[34] In three studies, there was not significant improvement in SCIT versus control.[29, 35, 37]

The eight studies of HDM allergen included six in adults and two in mixed populations.[34, 37, 38, 43-45, 55, 56] In three studies, asthma severity was not reported, two included mild and moderate asthma, one stated that all severities were included, one stated that patients were controlled and in one patients were poorly controlled. In six of the studies, there was significant improvement in AHR compared with control, in one the improvement was demonstrated in the SCIT group but not in the control group, and in one there was no significant difference in AHR with control. Treatment durations ranged from seven weeks to two years. The study that did not show improvement in AHR was of seven months duration.

Of the two studies of cat allergen, one study showed improvement in AHR.[36] This study enrolled adults and asthma severity was not reported. Patients were monosensitized to cat allergen and were treated for at least one year. In the other study of cat allergen, there was not improvement in AHR.[35] In this study of adults with controlled asthma, patients who were monosensitized to cat allergen were treated for 16 weeks.

For the study of dog allergen challenge, there was not improvement in AHR.[29] This study enrolled mixed age patients with monosensitization to dog allergen. Asthma severity was not reported. Treatment was for one year.

The study of cladosporium allergen showed significant improvement in AHR with allergen challenge after a duration of 10 months treatment.[52] This study enrolled mixed age patients with mild to moderate asthma that was controlled.

In the study of ragweed allergen, adults with moderate to severe, uncontrolled asthma were enrolled.[53] Patients had to have had exacerbations of asthma during the fall season. Significant improvement in AHR was shown after two years of treatment. (Appendix D - Table 10 for details.)

Exercise challenge. No SCIT studies reported exercise challenge outcomes.

Compliance

One study comparing multiple allergen SCIT to placebo in 121 children reported that both arms had high levels of compliance (measured at each visit on the basis of prescribed doses and doses recorded in diaries) (92.6 versus 93.6 percent) and there was no difference between arms.[31]

Immunological Outcomes

Allergen testing. Five RCTs reported allergen skin testing results before and after SCIT.[28, 32, 46, 48, 57] Four studies exclusively looked at skin test reactivity to HDM[28, 46, 48, 57] and one study examined mixed reactivity to multiple allergens including HDM, mold, trees, animals and grass.[32]

Only one study did not find any differences in skin prick testing for HDM between SCIT and placebo over a 3 year period.[46] Four studies report significant improvement in allergen skin reactivity after SCIT using different skin testing parameters;[28, 32, 48, 57] one that used cutaneous tolerance index reported improvement over a period of 15 weeks for HDM (95% CI 0.27; 0.11-0.56, $P<0.05$).[48] Two studies using histamine equivalent skin test reaction found statistically significant improvement in multiple intradermal skin testing parameters including immediate phase ($P=0.04$) and late phase skin reactions ($P=0.002$) in addition to skin prick titration tests to determine the estimated allergen concentration that caused histamine equivalent skin reactions ($P=0.0001$)[28] and demonstrated improved histamine equivalent skin test reactions for HDM over 54 weeks ($P=0.029$).[57] Lastly, the study using multiple allergens reported general improvement in skin testing parameters for mixed allergens for 1 year in SCIT patients compared to placebo ($P=0.0001$).[32]

Overall risk of bias was low in one study and moderate in four. The five studies included 495 patients and four were used HDM allergen. Treatment ranged from 1 to 3 years. The administration of SCIT was associated with improvement in allergen skin reactivity, mainly with HDM.

Immunoglobulin E. Eight RCT studies reported IgE levels of which six studies examined HDM,[28, 30, 46, 48, 57, 58] one study examined alternaria,[41] and one study looked at mixed allergens for HDM, mold, trees, animals, grass.[32] Six studies demonstrated significant reductions in IgE levels after SCIT.[28, 32, 41, 46, 58] [30]Four studies demonstrated statistically significant decreases in serum IgE levels for HDM from 1-3 years in the SCIT group compared to either placebo, desensitization vaccine (not specific desensitization

method), ICS or untreated patients.[28, 46, 58,30]Two studies demonstrated significant reductions in IgE for alternaria and mixed allergens, respectively, when SCIT was compared to pharmacotherapy.[32, 41] Two studies showed no change in total IgE after treatment.[48, 57]

Immunoglobulin G4. Four SCIT RCTs reported serum IgG4 levels specific for HDM.[30, 40, 48, 57] all of which demonstrated statistically significant reduction of IgG4 levels. Two studies compared SCIT versus placebo for 15 weeks and 1 year.[48, 57] One study compared SCIT to standard pharmacotherapy[40] while another examined SCIT and inhaled corticosteroids versus inhaled corticosteroids alone.[30] One study reported a significant decrease in the HDM specific IgE/IgG4 ratio in patients undergoing SCIT compared to placebo.[57]

Variation per Setting

Three studies did not specify setting.[41, 46, 54] All other studies (n=28) were done in the clinical setting and no study was conducted in the home setting. There are no data to draw conclusions on any variation per setting.

Variation per Population

Adults

Asthma symptoms. No studies in adults reported on asthma symptom outcomes using ACT, ACQ or P-ACT scores.

Quality of life. Two studies in adults assessed quality of life with AQLQ. Both studies showed statistically significant improvement in quality of life with SCIT compared to control.[43, 44] These studies included adults with mild and moderate persistent asthma, and they were treated with HDM allergen for 54 and 55 weeks.[43, 44] The differences in overall AQLQ were approximately 4 points (P=0.043) and 6 points (P=0.0025), respectively. These studies of adults were both positive and SOE was moderate with consistent and precise results and medium risk of bias.

Medication use.

Quick relief medications. One study of adults receiving HDM SCIT reported decrease in quick relief medication use (short acting beta agonists).[45] This study included 31 patients with unspecified asthma severity or control at baseline. The study reported a statistical significant reduction in medication use among those receiving SCIT (decrease from 27 to 14 puffs/week, P<0.05), and a non-significant reduction in the control group (decrease from 52 to 46 puffs/week, P NS). There was a substantial change in the use of medications but the duration of treatment was not clear from the study report. Overall, SOE was low for the effect of SCIT on quick relief medication use, based on one small study (n=31) (imprecise, unknown consistency) with low risk of bias.

Long term control medications. Two studies in adults evaluated the effect of SCIT on use of long term control medications. One study of adults with mild asthma showed statistically significant reduction in long term control medication use in the SCIT group when compared to placebo.[43] This study reported a greater number of weeks free from inhaled corticosteroids use in SCIT compared to placebo (P<0.001). This was a study of 64 patients with mild or moderate persistent asthma, treated with HDM allergen. Another study of adults[45] reported a significant reduction in inhaled corticosteroids dose in the SCIT group during the study (38%, P <0.05) and a non-significant change in the control group. This study enrolled 31 patients with unspecified baseline asthma severity and control. For the subgroup of adults,

SCIT may reduce long term medication use, based on consistent results from two small studies (imprecise) (low SOE).

Systemic corticosteroids. There were no studies of the effect of SCIT on systemic corticosteroids in adults.

Asthma exacerbations. There were no studies of the effect of SCIT on asthma exacerbations in adults.

Healthcare utilization. There were no studies of the effect of SCIT on health care utilization in adults.

Pulmonary physiology.
PEF. Two studies in adults, showed significant improvement in PEF. In one study of HDM allergen in 16 adults,[34] morning PEF improved significantly in the SCIT group but not the controls. In this study, treatment was for 6 months and the asthma patients were controlled at baseline. In the other study of adults, 90 patients were studied who had uncontrolled asthma at baseline. Ragweed allergen was used and there was a significant difference in PEF between SCIT and control, when measured in the morning during the peak allergen season.[53]

FEV_1. Only one study in adults assessed FEV_1 and it reported significant changes within SCIT arm but not for placebo ($P<0.001$ vs $P>0.05$) but did not directly compare the groups.[54]

FEV_1/FVC. There were no studies of the effect of SCIT on FEV_1/FVC in adults.

FVC. There were no studies of the effect of SCIT on FVC in adults

Airway hyperresponsiveness. There were nine studies performed in adults that assessed the effect of SCIT on allergen challenge. Of these six done with HDM allergen, two cat and one ragweed.[34, 35, 45, 53, 55, 56] Of these studies in adults, all showed improvement in AHR compared with control, except one that only showed improvement in the SCIT group but not control and one study that showed no significant difference. Studies of SCIT in adults that examined AHR by specific allergen challenges had consistent and precise results supportive of improvement.

Compliance. There were no studies of the effect of SCIT on compliance in adults.

Children

Three studies including 403 children reported on the efficacy of SCIT for clinical outcomes in children ages 5-12 years with asthma. One study was completed in the US,[31] and two were completed in Asia.[32, 49] Asthma diagnosis was per GINA criteria in two of the studies,[32, 49] and not specified in the third.[31] Two studies included children with moderate to severe persistent asthma[31, 49] and one study excluded patients with severe uncontrolled asthma.[32] Allergy diagnosis was made by skin-prick testing and specific IgE elevation in all studies.[31, 32, 49] Two of the studies included polysensitized patients and used multi-allergen SCIT[31, 32] and one study enrolled patients monosensitized to HDM and used HDM SCIT.[49] One study compared SCIT to placebo,[31] and the other two studies compared SCIT to pharmacotherapy.[32, 49]

Asthma symptoms. There were no studies of the effect of SCIT on asthma symptom outcomes using ACT, ACQ or P-ACT scores in children.

Quality of life. There were no studies of the effect of SCIT on asthma quality of life using the AQLQ, Pediatric Asthma Specific Quality of Life, or school/work absences in children.

Medication use. One RCT that compared multiple allergen SCIT to placebo in 121 children reported number of days of medication use in the previous 60 days.[31] This study found a statistically significant decrease in the number of days of inhaled corticosteroid use in the SCIT arm but not in the placebo arm. However, there was no significant difference in the use of inhaled corticosteroids between arms. This study also reported that there was no significant difference within or between arms for the use of oral steroids. There is insufficient evidence on the effect of SCIT on asthma specific medication use in children.

Asthma exacerbations. There were no studies of the effect of SCIT on asthma exacerbations in children.

Healthcare utilization. As noted above, two RCTs reported on healthcare utilization in children with allergic asthma.[31, 49] Overall the strength of evidence is insufficient.

Pulmonary physiology.
*PEF***.** Two RCTs reported PEF in a total of 161 children.[31, 49] One RCT used HDM SCIT versus pharmacotherapy alone (asthma medications per GINA guidelines) and found that the PEF increased in the SCIT arm and decreased in the control arm however the change both within and between arms was not statistically significant.[49] The other RCT used multiple allergen SCIT versus placebo and noted a clinically small increase in PEF in the SCIT arm compared with placebo (95% CI -7.8 to 0.1, *P*= 0.05).[31]

FEV1. One RCT of multiple allergen SCIT versus pharmacotherapy alone (beclomethasone inhaler 200-300 µg daily and aminophylline 100mg tablet twice daily) reported FEV_1 in 242 children treated for 12 months and found that patients in the SCIT arm had significant improvement in their FEV_1 compared with the pharmacotherapy arm (*P*= 0.0001).[32] However, we are unable to draw conclusions due to insufficient evidence (unknown consistency, imprecise, medium risk of bias).

FEV_1/FVC. There were no studies of the effect of SCIT on FEV_1/FVC in children.

FVC. There were no studies of the effect of SCIT on FVC in children.

Airway responsiveness. One study comparing multiple allergen SCIT to placebo in 121 children reported methacholine challenge results.[31] Both arms had a significant decrease in bronchial sensitivity to methacholine but there was no difference between arms (mean difference -0.02 (95% CI -0.66 to 0.61) *P* >0.99).[31]

Compliance. One study comparing multiple allergen SCIT to placebo in 121 children reported that both arms had high levels of compliance (92.6 versus 93.6 percent) but the difference between arms was not reported.[31]

Table 3- Summary of the Strength of Evidence for the Efficacy of Subcutaneous Immunotherapy

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	Strength of Evidence
Asthma Symptoms ACT	No RCTs	NA	NA	NA	NA	Undetected	Unable to draw conclusions	Insufficient
Quality of Life AQLQ	4 RCTs.[41-44] N=194	Medium	Consistent	Direct	Imprecise	Undetected	SCIT may improve asthma-quality of life	Low
Medication Use Quick relief medication	1 RCT [45] N=31	Low	Unknown	Direct	Imprecise	Undetected	SCIT may reduce the use of quick relief medications	Low
Medication Use Long term medication	5 RCTs [40, 42, 43, 45, 46] N=283	Medium	Consistent	Direct	Precise	Undetected	SCIT reduces the use of long term control medications	Moderate
Medication Use Systemic Corticosteroids use	2 RCTs[31, 47] N=150	Low	Unknown	Direct	Imprecise	Undetected	SCIT may reduce the use of systemic corticosteroids	Low
Healthcare Utilization	2 RCTs [31, 49] N=161	Medium	Consistent	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient
Pulmonary Physiology FEV1	6 RCTs[32, 41, 42, 51, 55] N=548	High	Consistent	Direct	Precise	Undetected	SCIT may improve pulmonary function when measured with FEV1	Low

FEV1 – Forced Expiratory volume

Key Question 2. What is the evidence for the safety of subcutaneous immunotherapy (SCIT) in the treatment of asthma?

Key Points

- Local reactions to SCIT were frequent; however, reactions also commonly occurred with placebo injections (risk differences ranged from -0.317 to 0.4), and local reactions infrequently required a change in the SCIT dosing.
- Systemic reactions to SCIT were reported frequently (risk differences ranged from 0 to 0.319). The majority of systemic reactions were mild, and only a small number was consistent with anaphylaxis and required treatment with injectable epinephrine. Systemic reactions did not appear to occur more commonly in patients receiving an accelerated SCIT protocol compared to conventional SCIT protocols.
- There was insufficient evidence to draw conclusions regarding effect of SCIT on anaphylaxis or death.
- Serious adverse events such as anaphylaxis and death were not reported in the included studies in the pediatric population (total of 462 patients in four RCTs).

- None of the studies reported providing patients SCIT in the home setting.

Overall Study Characteristics

Our search identified a total of 42 articles on 40 unique studies/populations reporting safety data on SCIT. Of the included studies, 26 were RCTs (28 articles), and 16 were either cohort, case-control, or case reports. Of all studies included (RCTs and non-RCTs) 19 included adults, 19 included a mixed age population and four included children. The articles were published between 1984 and 2015, with 52 percent of studies originating from Europe, 21 percent from Asia, and 21 percent from the US.

Details on study, patient characteristics, and interventions are provided in Appendix E and components in the assessment of risk of bias are shown in Appendix I.

Summary and Description of Characteristics in RCTs

Of the 26 RCTs (N=1,512), 12 studies enrolled only adults (defined as age greater than 12 years of age), [28, 34-36, 43, 44, 48, 53-57, 59, 60] ten enrolled mixed age populations,[29, 30, 38, 40, 42, 46, 52, 61-63] and four children only.[19, 29, 31, 32, 46, 49] SCIT was compared to placebo in 15 studies,[28, 29, 31, 34-36, 38, 43, 44, 48, 52-55, 57, 61, 63] to pharmacotherapy in six studies,[30, 32, 40, 42, 49, 56] and to SCIT in a modified dose or duration in five studies.[19, 46, 59, 60, 62]

GINA criteria were used for asthma diagnosis in 10 studies; [19, 28, 30, 32, 40, 44, 49, 52, 59, 60, 62] a positive bronchial response to methacholine was used in two studies,[53, 55] to histamine in one study,[34] to cat allergen in one study,[35] and HDM allergen in one study.[56] The diagnosis was clinical or not specified in the remaining 10 studies.[29, 36, 38, 42, 43, 46, 48, 54, 57, 61, 63, 64]

Asthma was classified as mild or moderate persistent in 14 studies;[19, 28, 32, 38, 40, 42-44, 46, 48, 52, 57, 59-62] three studies included patients with severe persistent asthma, [49, 53, 63] and in nine studies the severity was not classified.[29-31, 34-36, 54-56] Asthma control status prior to initiation of SCIT was described in six studies: asthma was reported as controlled in four studies,[34, 35, 52, 62] and uncontrolled on poorly controlled in two studies.[38, 53]

Documentation of allergic sensitization was made through skin prick testing and/or serum IgE in all studies.

Patients were monosensitized in 14 studies and polysensitized in five studies. [28-32] One study included both polysensitized and monosensitized patients,[19] and six studies did not clearly report sensitization status.[34-36, 38, 40, 62] Patients received single allergen immunotherapy in 23 studies and multiple allergen immunotherapy in three studies.[28, 31, 32, 59] The allergen provided included HDM in the majority (60%) of studies. Other allergens were grass, ragweed, cat, cladosporium mold, and dog. In the three studies where multiple allergens were provided, the type of allergen was not specified. In 24 studies, SCIT was provided in the clinic setting; the location was not specified in two studies.[46, 54]

Adults. Of the 26 RCTs, 12 studies enrolled only adults. [28, 34-36, 43, 44, 48, 53-57, 59, 60] SCIT was compared to placebo in all studies except for two studies where it was compared to pharmacotherapy,[28,56] and one study where it was compared to a modified SCIT (a depigmented-glutaraldehyde polymerized extract).[60]

GINA criteria were used for asthma diagnosis in three studies;[28, 44, 59, 60] a positive bronchial response to methacholine was used in two studies,[53, 55] to histamine in one study,[34] to cat allergen in one study [35] and HDM allergen in one study.[56] The diagnosis was clinical or not specified in four studies.[36, 43, 48, 54, 57]

Asthma was classified as mild or moderate persistent in 5 studies,[28, 43, 44, 48, 57, 59, 60] one study included patients with severe asthma [53] and in six studies the severity was not classified.[34-36, 54-56]Asthma

control status prior to initiation of SCIT was described in three studies: asthma was reported as controlled in two studies.[34, 35] and uncontrolled on poorly controlled in one study.[53]

Documentation of allergic sensitization was made through skin prick testing and/or serum IgE in all studies. Patients were monosensitized to a single allergen in all except for one study where patients were polysensitized.[28, 59] In all studies except for one,[28, 59] a single allergen was provided in SCIT. The allergen provided included HDM in 50 percent of studies. Other allergens were grass, ragweed, and cat. In the studies where multiple allergens were provided, the type of allergen was not specified.

Children. Four RCTs reported on the safety of SCIT in 466 children with asthma. Studies included children with moderate and severe persistent,[49,31] mild and moderate persistent asthma[19] and one specifically excluded those with uncontrolled asthma.[32] In two studies, patients had at least an allergy to HDM and HDM SCIT was used in the trial.[19, 49] Two studies included polysensitized patients and used multiple allergen SCIT.[31, 32] Two studies compared SCIT to pharmacotherapy alone,[32, 49] one compared SCIT to placebo[31] and one study compared three year to five year SCIT.[19]

Summary and Description of Characteristics in Non-RCTs

Of the 16 non-RCTs, seven studies included adults only (defined as age greater than 12 years)[21, 22, 24, 65-68] and 9 mixed age populations. [20, 23, 25-27, 69-72]

SCIT was provided in a cluster, rush, or ultra-rush protocol in 6 of the 16 studies (38%).[21, 22, 25, 26, 67, 71] Documentation of allergic sensitization was made through skin prick testing and/or serum IgE in 8 articles [20, 65-69, 71, 72] otherwise it was not specified. Allergen identified was not reported in seven studies,[21, 22, 24, 25 844, 27, 66, 70] four studies had monosensitized patients,[26, 68, 69, 72] two polysensitized,[23, 71] two both poly and monosensitized,[20, 65] and one study did not clearly report sensitization status.[67] Nine studies treated with single allergen and seven with multiple allergens.

Adults. SCIT was provided in a cluster, rush, or ultra-rush protocol in three (43%) of seven studies. [21, 22, 67] Documentation of allergic sensitization was made through skin prick testing and/or serum IgE in four articles [65-68] otherwise it was not specified. Two studies included polysensitized patients, one monosensitized patients, one both poly and monosensitized and four studies did not specify. In four studies patients were treated with multiple allergens. Four of the studies were case reports. [22, 24, 66, 68] (See Appendix F for further details.)

Children. There were no non-RCTs assessing safety of SCIT in pediatric population.

Hypersensitivity

Studies did not specifically report on “hypersensitivity reactions”. However, it is well known that the vast majority of systemic (and some local) reactions fall under the umbrella of hypersensitivity reactions to the allergens. The individual reactions will be discussed in their respective RCT and non-RCT categories.

Local Reactions

Summary and Description of Events in RCTs

Local reactions consisting of itching, pain, paresthesia, heat, erythema and induration, at the site of injections were reported in 6.25 percent [43] up to 33.3 percent [30] of patients. Notably, local reactions occurred with the placebo injections in zero up to 12.5 percent of patients. [35, 43, 48] Calculated risk differences ranged from -0.317 to 0.4. That is, a range of from 32 additional cases of local reactions in

the placebo group to 40 additional cases per 100 people treated with SCIT).) In one study, patients who received SCIT to dog allergens had 20 episodes of local swelling per patient, as compared to 21 episodes per patient in those receiving placebo injections(calculated risk difference -0.317),[29, 64] compared to one study with HDM, in which eight patients who received HDM SCIT presented local swelling at injection site, as compared to none of the patients receiving placebo (calculated risk difference 0.4).[49]

Adults. Local reactions described as local erythema, induration, at the site of injections were reported in 6.25 percent [43] up to 22 percent[35] of patients. In the latter report,[35] 2 of 9 patients (22 percent) had three large local reactions severe enough to require modifications of the immunotherapy schedule, while none of the placebo patients has similar reactions. Local reactions were described with placebo injections in zero to 12.5 percent of patients.[35, 43, 48]

Children. One study reported local red swelling at the site of HDM SCIT injection in eight children (calculated risk difference 0.4).[49]

Summary and Description of Events in Non-RCTs

Local reactions described as swelling or urticarial plaques at the site of injections were reported in 4 studies, and ranged from 5.6 to 27.3 percent of patients treated,[21, 23, 67] and in 6.5 to 10.7 percent of SCIT doses given.[21] In the study in which the size of the local swelling was reported, 10.1 percent had a small reaction (<5 cm in diameter) and 13.2 percent had a large reaction (≥ 5 cm in diameter).[23]

Adults. Local reactions consisting of swelling or urticarial plaques at the site of injections were reported in 5.6 to 27.3 percent of patients, [21, 67] and in 6.5 to 10.7 percent of SCIT doses given.[21] One patient developed multiple subcutaneous itchy nodules on the lateral aspects of both arms, at the site of previous immunotherapy injections to timothy grass pollen.[24]

Children. There were no non-RCTs assessing local adverse events of SCIT in pediatric population.

Systemic Reactions

Summary and Description of Events in RCTs

Systemic reactions were described in 16 studies, including 540 patients treated with SCIT compared to 182 patients treated with placebo injections and 265 patients treated with pharmacotherapy. In four studies there were specifically no systemic reactions reported. The rate of systemic reactions ranged from zero to 44 percent of patients (4 out of 9 patients receiving SCIT for cat);[35] when reported as number of injections, the highest rate of systemic reactions was 11.7 percent of total injections given (203 reactions out of 1735 total injections).[46] Types of reactions included pruritus, urticaria, eczema, skin rash, rhinitis, conjunctivitis, nasal congestion, nasal obstruction, cough, asthma, bronchospasm, wheezing, dyspnea, abdominal pain, diarrhea, and hypotension. However, in several studies the types of reactions were not specified, and were described as “Not specified”, “Mild systemic reaction”, “Mild-moderate systemic reaction”, “Systemic reaction”, “Systemic reaction requiring Epinephrine”, “unspecified symptoms”, and “pulmonary reactions”. The calculated risk differences based on the number of patients who developed systemic reactions ranged from 0 to 0.319.

Adults. Systemic reactions were described in eight studies, including 205 patients treated with SCIT, compared to 152 patients treated with placebo injections and 18 patients treated with pharmacotherapy. In two studies there were specifically no systemic reactions reported. The rate of systemic reactions

ranged from zero to 44 percent (4 out of 9 patients receiving SCIT for cat, calculated risk difference 0.319).[35] Out of the patients receiving SCIT, 46 patients were receiving an accelerated SCIT protocol (rush or cluster protocol).

There were 36 patients receiving SCIT who developed systemic reactions, as compared to 6 patients receiving placebo injections. Out of these 36 patient, 7 patients were receiving an accelerated protocol.[55, 56] The description of the nature and severity of these systemic reactions varied greatly from study to study.

Children. Three studies reported systemic reactions. Two studies used multiple allergen; one compared multiple allergen SCIT to pharmacotherapy; it reported that nine children (11%) in the SCIT arm had an immediate systemic reaction.[32] One of these children had mild respiratory involvement (grade 2) and eight had a skin rash (grade 1), all reactions were successfully treated in the clinic and did not require additional observation or hospitalization. The reactions and subsequent treatment were not described in further detail.[32] The other study compared multiple allergen SCIT with placebo; it reported systemic reactions to injections in 21 of the 61 children in the SCIT group (34%) and in 4 of the 60 in the placebo group (7%) (P =0.001). In this study with 121 children, there were 114 total systemic reactions (in 21 of the 61 children receiving SCIT and 4 of the 60 children receiving placebo), 52 of which were treated with adrenergic drugs; however, the severity of the reactions, or the type of adrenergic drugs used, was not specified, and there were no dropouts due to reactions to SCIT. All 52 responded to treatment, without clinical sequelae.[31] In one study that compared 3 years versus 5 years of HDM SCIT, two patients with asthma in the 5 year arm had an asthma episode within 30 minutes of receiving a maintenance dose that resolved with a bronchodilator. The following dose was adjusted in both patients and the authors comment that long-term tolerance was confirmed in every patient.[19] One study specifically commented that there were no systemic reactions.[49]

Summary and description of events in non-RCTs

Systemic reactions were described in 13 studies (see Appendix G), seven were case series and two were single case reports.[22, 68] The rate of systemic reactions ranged from 0.6 percent of patients and 0.1 percent of injections[27] to 23.9 percent of patients;[20] in the latter study, 16 of 67 (24%) children receiving SCIT to HDM developed "non-fatal systemic reactions". Reported systematic reactions consisted of urticaria, asthma, flushing, nasal congestion, nasal itching, wheezing, chest tightness, bronchospasm, vasculitis, and anaphylaxis. However, in several studies the types of reactions were not specified, and were described as "Non-specified systemic symptoms", "systemic reactions", "systemic effects" and "non-fatal systemic reactions".

In the studies where systemic reactions and numbers of patients treated were reported, the total number of patients treated with SCIT was 5692 patients, 52 patients treated with pharmacotherapy, and no patients treated with placebo injections. Out of the patients who received SCIT, 311 were being treated with a cluster regimen,[21, 22, 25] and 836 were being treated with a rush or ultra-rush regimen.[26, 67, 71]

Adults. Systemic reactions were described in five studies of adults, two of which were single case reports.[22, 68] The rate of systemic reactions ranged from 1.5 percent of patients [21] to 11 percent;[65] in the latter study, patients were treated with SCIT to HDM and animals, and the highest rate of systemic reaction was in patients with asthma but without seasonal rhinitis (11%) (as compared to patients with asthma and seasonal rhinitis where the rate of systemic reactions was 3%). In the studies where systemic reactions and numbers of patients treated were reported, the total number of patients treated with SCIT was 379 patients, with no patients being treated with placebo injections or pharmacotherapy. Out of the

patients received SCIT, 184 were being treated with a cluster regimen [21, 22] and 18 were being treated with a rush or ultra-rush regimen.[67]

Excluding case reports, there were 20 patients receiving SCIT who were reported to have systemic reactions. Six of these patients were receiving an accelerated SCIT protocol. The case reports described one patient who developed anaphylaxis treated with epinephrine, and one patient who developed leukocytoclastic vasculitis that occurred repeatedly after SCIT injections.

Children. One study that included 67 children with asthma and allergic rhinitis sensitized to HDM who received HDM SCIT for two years documented that systemic reactions occurred in (16/67) 23.8 percent of children with asthma (27/2045 or 1.32% of total injections). All children in this study completed the initial phase of SCIT. Not all patients had asthma in this study and the systemic reactions were not described further for children with asthma specifically.[20]

Anaphylaxis

Summary and description of events in RCTs

Only one RCT specifically reported anaphylaxis, reporting that there were no anaphylaxis events amongst 33 patients who received SCIT to HDM.[30] This RCT was conducted in 65 people and was considered at medium risk of bias.

Upon review of the nature of reactions in all of the SCIT RCTs four of the remaining 25 RCTs had patients with reactions we considered consistent with anaphylaxis.[40, 53, 55, 60](See Table A.4 in Appendix E). One trial compared different forms of SCIT, reporting that one out of 12 patients receiving unmodified SCIT to grass developed urticaria, and bronchospasm compared to none of the 11 patients in the modified SCIT arm.[60] In another trial at high risk of bias, one patient in the placebo group (n=40) received a SCIT injection to HDM by mistake, and developed bronchospasm and hypotension requiring epinephrine.[53]

One RCT, at high risk of bias due to lack of allocation concealment and masking of outcome assessors, reported a high rate of anaphylaxis with 3 of 20 patients receiving rush HDM SCIT having a reaction consistent with anaphylaxis and none of the 10 patients receiving placebo injections having such a reaction (risk difference of 0.15). [55] The rush SCIT protocol was delivered over the course of 3 to 4 days, starting at 30 BU of Dpter. Once maintenance was reached, patients received weekly injections of 3000 BU. Four patients experienced a “systemic reaction” during the rush protocol, and three of these patients required epinephrine injections. The underlying asthma severity in these patients was not reported. No systemic reactions occurred while patients were on maintenance SCIT, and no systemic reactions occurred in the placebo group.

Finally, one RCT, judged to be at low risk of bias, randomized 50 patients to receive either SCIT to HDM (15 patients), SCIT to HDM in addition to oral vitamin D (17 patients), or pharmacotherapy only (18 patients). [40] One patient in the SCIT-alone group experienced a systemic reaction within 20 minutes after injection of vial 4 during the buildup phase and was treated with epinephrine. Two patients in the SCIT+Vitamin D group developed mild asthma attacks, and were treated with inhaled beta-2 agonist. The underlying asthma severity in these patients was not described. The risk difference, comparing the SCIT groups versus placebo, is 0.03.

Overall, the reports of systemic reactions consistent with anaphylaxis varied greatly (from 0 to 15 additional cases of anaphylaxis per 100 people treated with SCIT). We are unable to draw conclusions on whether SCIT increased risk of anaphylaxis primarily because the RCTs did not directly measure or report anaphylaxis (indirectness), and were not powered to assess such effects (imprecision).

Adults. As described above, one RCT reported three out of 20 patients receiving rush SCIT to HDM were treated with epinephrine due to reactions consistent with anaphylaxis.[55] One out of 12 patients receiving SCIT to grass developed urticaria, and bronchospasm.[60]

Children. There were no RCTs of SCIT assessing or reporting anaphylaxis in pediatric population.

Summary and description of events in non-RCTs

A case series with a total of 658 patients, reported no cases of anaphylaxis in 339 patients (2712 doses) receiving cluster SCIT, and 319 patients (2552 doses) receiving conventional dosing SCIT with multiple allergens.[21]

One case series reported specifically on the incidence of "anaphylaxis" in patients with mixed age groups.[70] In this study, anaphylaxis was classified as "mild, moderate, or severe" based on symptoms. Reactions were classified as uniphasic (symptoms occurred within 5-30 minutes and resolved gradually), or biphasic (initial symptoms resolved then the re-emerged within several hours). There was a total of 453 patients receiving SCIT for allergic rhinitis, asthma, or venom allergy; 133 patients had asthma. A total of 21,022 injections were given and 131 anaphylactic reactions were recorded in 76 out of the 453 patients (120 uniphasic and 11 biphasic); 65 of these reactions were treated with epinephrine. The total incidence of anaphylaxis was calculated as 1.3%. Out of these 131 reactions, 63 (48%) occurred in patients who had asthma; however the severity of systemic reactions in patients with underlying asthma was not described. Following WHO criteria for assessing case reports, we determined that SCIT causing the anaphylaxis reactions reported in this case series (causality) was likely.

Adults. A case series with a total of 658 patients-5264 doses with multiple allergens (cluster vs conventional) reported no cases of anaphylaxis.[21] One case report described a patient receiving cluster grass SCIT who presented chest tightness with wheezing requiring epinephrine.[22]

Children. There were no non-RCTs of SCIT assessing anaphylaxis in pediatric population

Deaths

Summary and description of events in RCTs

No deaths were reported in the RCTs.

Summary and description of events in non-RCTs

There was one case report [66] of death occurring in a 17 year-old female with moderate persistent asthma who had received SCIT in childhood for 4 years and stopped due to a mild skin reaction. At the age of 16, she was restarted on a regimen of SCIT for pollens, that she tolerated well for one year. The authors report that 12 hours after she received a SCIT injection, she complained of abdominal pain, vomiting and diarrhea without fever and was hospitalized. Two days later, she developed an acute respiratory failure and was transferred to the intensive care unit, where she was found to have multiorgan failure; she had markedly elevated creatine phosphokinase, elevated troponin, leukopenia, thrombocytopenia, and bilateral interstitial markings on chest X-ray. On day 4 she developed hypoxic coma leading to intubation and mechanical ventilation, and by day 5 had rapid development of shock and acute renal impairment leading to death. The authors reported that her reaction "may probably result from an immunological mechanism…probably the consequence of an error of manipulation and/or the escalating of the dosing regimen of the product". Following WHO criteria for assessing case reports, we determined that the likelihood of SCIT causing this death (causality) was unlikely based on the timing

and the nature of the reaction. The patient had been receiving SCIT for one year without problems, and started to develop symptoms that were delayed (12 hours) following a SCIT injection; there was no mention whether she had received a different or escalating dose. The nature of her clinical presentation, with markedly elevated creatine phosphokinase and troponin, are not suggestive of a hypersensitivity reaction.

Variation per setting

Of the 26 RCTs, SCIT was provided in the clinic setting in 24 studies, and two studies did not specify the location. There were no studies reporting administration of SCIT at home. Therefore, in all the studies where location was mentioned, SCIT was provided in the clinic setting. There is insufficient evidence to analyze any variation in adverse effects of SCIT by the clinic or home setting.

Table 4- Summary of the Strength of Evidence for the Safety of Subcutaneous Immunotherapy-SCIT

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	Strength of Evidence
Anaphylaxis	5 RCTs[30, 40, 53, 55, 60] N=245 6 cases	Medium	Inconsistent	Indirect	Imprecise	Undetected	Unable to draw conclusions	Insufficient
	1 Non-RCT[70] 1case series[21] 1 case report.[22] N=792 55 cases	Likely (Likelihood of causality)						
Death	No RCTs or Non-RCTs						Unable to draw conclusions	Insufficient
	1 case report[66]	Unlikely (Likelihood of causality)						

Key Question 3. What is the evidence for the efficacy of sublingual immunotherapy (SLIT), in tablet and aqueous form, for the treatment of asthma?

Key Points

- SLIT improves asthma symptoms as measured by validated instruments (high SOE).
- SLIT improves disease specific quality of life, and decreases use of long term control medications (specifically inhaled corticosteroids) (moderate SOE).
- SLIT may decrease quick relief medication use (short acting bronchodilators), and improve FEV_1 (low SOE).
- There is insufficient evidence on the effect of SLIT on systemic corticosteroid use, or healthcare utilization.

- There is insufficient evidence about the efficacy of SLIT in children.

Overall Study Characteristics

We identified 16 RCTs regarding the efficacy of SLIT for asthma. The articles were published between 2001 and 2016, with 75 percent of the articles originating from Europe. Ten studies included only adults,[73-82] three studies included mixed adult/children populations.[83-85] and three studies included only children.[86-88] Patients were monosensitized in 11 studies and polysensitized in one study.[77] Four studies included both polysensitized and monosensitized patients,[73-75, 83] The majority of studies treated HDM allergy, followed by birch and grass. No study used multiple allergens.

Details on study, patient characteristics, and interventions are provided in Appendix F and components in the assessment of risk of bias are shown in Appendix I.

Asthma Symptoms

Asthma symptom control outcomes were reported in four SLIT RCTs[73, 74, 76, 77] which included a total of 1193 patients, with all studies including adult patients. Clinically and statistically significant improvement in scores was found in 3 of 4 studies.[74, 76, 77] Three studies were low risk of bias, and the fourth had medium risk of bias.

Three studies used HDM in comparison to placebo, and utilized the Asthma Control Questionnaire (ACQ) to evaluate asthma symptoms.[73, 74, 77] The treatment duration for all three HDM studies was one year, with daily maintenance dosing ranging from 1 SQ-HDM to 12 SQ-HDM, or 300IR for the daily dose. Two studies utilized tablets,[73, 74] and one aqueous drops.[77] Two of the three HDM studies were performed in patients with mild-moderate persistent asthma and demonstrated statistically significant improvement in asthma symptoms with SLIT with daily maintenance doses or 6SQ-HDM tablet and 300 IR drops.[74, 77] One RCT found statistically significant improvement in a subgroup analysis of 180 moderate persistent asthmatics (percentage improvement 56% versus 40%, $P<0.039$); this effect was not found in the mild asthmatics.[74, 77] The second RCT found statistically significant improvement in asthma symptoms (p=0/0002), with a decrease of 0.41 in ACQ score in the 6 SQ-HDM treatment group, compared to no change in score in the control group.[74, 77] The third HDM study was performed in patients with moderate to severe asthma and did not demonstrate statistically significant improvement ($P=0.22$).[73] The doses that were shown to be effective in studies with statistically significant improvement were 300 IR and 6 SQ-HDM.

The fourth study of asthma symptoms used birch allergen with a maintenance dose of 100 AU tablet 5 days per week for 3 years plus daily inhaled budesonide 400 µg daily, and the Asthma Control Test (ACT) to assess asthma symptoms outcomes.[76] The comparator was treatment with inhaled budesonide (800 µg daily, 1600 µg daily, or 400 µg inhaled budesonide plus montelukast 10 mg daily). Treatment with birch allergen for 3 years in this study resulted in a statistically significant improvement of ACT scores (mean post value 24 in SLIT arm, versus 18 in other arms, $P<0.05$).

There is high strength of evidence that SLIT improves asthma symptoms, based on a body of evidence that is consistent in the direction of change, precise, direct, with an overall low risk of bias.

Quality of Life

Three RCTs, all of HDM allergen with a total of 1120 patients, examined the impact of SLIT on disease specific quality of life utilizing the AQLQ.[73, 74, 77] Two studies were low risk of bias, and one medium. All three studies included only adult patients and each compared SLIT with placebo.

One RCT reported statistically significant improvement in the AQLQ with SLIT when compared to controls (P=0.01), with an improvement of 0.52 in score compared to 0.0 for controls.[74] However, two other RCTs did not demonstrate statistically significant improvement (P =0.89, P reported as "not significant").[73, 77] The largest study (n=877) reported that scores in both SLIT groups and the placebo group improved but there was no statistically significant difference between SLIT and placebo.[73] Of the studies without statistically significant improvement, one included mild-moderate asthmatics, and the other study moderate to severe asthmatics. Two of the three RCTs utilized tablets[73, 74] and one aqueous drops.[77] All studies treated for one year, with daily maintenance dosing ranging from 1 SQ-HDM-12 SQ-HDM, or 300IR for the daily dose. The RCT that reported statistically significant changes in AQLQ used a 6 SQ-HDM tablet.[74]

The strength of evidence is moderate for the use of SLIT in improving asthma disease specific quality of life, based on a body of evidence that is consistent in the direction of change, precise, direct, and with an overall low risk of bias.

Medication Use

Quick relief medications. Four studies of SLIT reported quick relief medication outcomes in doses of SABA over 3 months, with three studies demonstrating statistically significant decrease in the need for SABA.[76, 81, 82] The studies were performed in patients with mild to moderate asthma, and included a total of 238 patients. The risk of bias was low for one study, medium for one, and high for the remaining study. The high risk of bias was due to lack of allocation concealment and blinding.[82] Two studies were performed in adults with birch allergy, treating for 5 years continuously (maintenance dose 3 times per week, 5 drops of 10,000 RU/ml; cumulative annual does of 70 micrograms of Phl p 1), or 3 years of pre/co-seasonal treatment (1000 AU tablet maintenance dose 5 days per week).[76, 81] The first birch SLIT study measured SABA use in doses during 3 month pollen seasons per year over 5 years, finding that in the SLIT group the number of doses on average dropped by 16.1, compared to control group which was treated with montelukast which decreased by 3.6 (P=0.019).[81] The second birch SLIT study measure SABA use over three month pollen seasons per year for 3 years, finding that the SLIT group decreased SABA intake on average by 10.1, in comparison to the control groups treated with inhaled budesonide (800 or 1600 µg, or inhaled budesonide 400 µg daily plus montelukast 10 mg daily) which had decreases of 0.7, 2.9, or 4.5 (P<0.001).[76] One study was performed with grass mix for 5 years (5 drops of 10,000 AU maintenance dose 3 times per week; cumulative annual dose for 100 micrograms of Bet v 1) The grass mix study measured doses of SABA over 3 month pollen season per year for 5 years, and found an average decrease of 17.9 in the SLIT group, compared to 9.4 in the control group treated with 800 micrograms daily of inhaled budesonide (P=0.01).[82] The fourth study was performed in children with HDM (20 drops of 300 IR/ml two time a week maintenance dose) and measured puffs of SABA per day, and did not find a significant change comparing SLIT to the placebo group after treatment (P=0.951).[87]

Overall, we found low SOE that SLIT may decrease the use of quick relief medications, based on a body of evidence that is consistent, imprecise, direct, and with an overall medium risk of bias.

Long term control medications. Four studies of SLIT reported long term control medication use, and included a total of 1308 patients. All studies treated mild to moderate persistent asthmatics with HDM, and evaluated the use of inhaled corticosteroids compared to placebo.[74, 77, 84, 87] Two studies were low risk of bias, and two medium. Two studies were performed in adults,[74, 77] one in mixed age populations,[84] and one in children.[87] Treatment duration ranged from 6 to 18 months, with dosing ranging from 1 SQ HDM to 12 SQ HDM, 100 IR, or 300 IR. The two studies performed in adults

demonstrated significant decrease in the used of inhaled corticosteroids with treatment using a daily maintenance dose of 300 IR drops or 6 SQ-HDM tablet.[74, 77] In the first of these two studies the authors measured absolute decrease in daily inhaled budesonide dose in micrograms, with the SLIT group decreasing by 218.5 on average, compared to the placebo group which decreased by 126.5 (P=0.004).[77] The second study reported the difference between placebo and SLIT in change from baseline in daily inhaled corticosteroid use in micrograms as 327 (P<0.0001).[74] The third study that included mixed age populations, used maintenance dose of 300 IR tablet, reported no statistically significant differences between SLIT and control.[84] The fourth study found no significant improvement in inhaled corticosteroid use measured in puffs per day when comparing SLIT to placebo (P=0.215).[87]

Two large studies with low to medium risk of bias demonstrated statistically significant improvement comparing SLIT to controls. We found moderate strength of evidence that SLIT decreases the use of long term control medications (inhaled corticosteroids). The strength of evidence was based on a body of evidence that is consistent in the direction of change, precise, direct, and with an overall medium risk of bias.

Systemic corticosteroids. One study reported on the effects SLIT on systemic corticosteroid use.[87] This study included only children and is discussed in the pediatric section below.

Asthma Exacerbations

Two studies reported on the effects of SLIT on asthma exacerbations using HDM in 1438 adult mild-moderate patients with persistent asthma.[73, 74] There were no children only or mixed aged population studies. One study, which utilized maintenance doses 6 or 12 SQ-HDM for 6 months in comparison to placebo, showed a statistically significant improvement in all of the following outcomes with the higher dose: time to asthma exacerbation, time to first asthma exacerbations with deterioration in asthma symptoms or nocturnal awakening, time to first exacerbation with deterioration in lungs function, time to first asthma exacerbation and use of SABAs, and time to first severe asthma exacerbations. These were reported as hazard ratios with SLIT compared to placebo, with the placebo group as reference. The hazard ratios for the 12 SQ-HDM dose in this study are as follows: time to first asthma exacerbation 0.69 (P=0.03), time to first asthma exacerbation with deterioration in asthma symptoms or nocturnal awakenings 0.64 (P=0.03), time to first asthma exacerbation with deterioration in lungs functions 0.52 (P=0.02), time to first exacerbation with increased use of SABA 0.52 (P=0.03), time to first severe asthma exacerbation 0.69 (P=0.02). The hazard ratios for the 6 SQ-HDM dose in this study are as follows: time to first asthma exacerbation 0.72 (P=0.45), time to first asthma exacerbation with deterioration in asthma symptoms or nocturnal awakenings 0.72 (P=0.17), time to first asthma exacerbation with deterioration in lungs functions 0.62 (P=0.03), time to first exacerbation with increased use of SABA 0.62 (P=0.09), time to first severe asthma exacerbation 0.72 (P=0.03).[73] However, the second study, which utilized 1, 3, or 6 SQ-HDM maintenance dose for one year in comparison to placebo did not find a statistically significant improvement in the number of asthma exacerbations; the authors did not report the data for asthma exacerbations in their article.[74]

Healthcare Utilization

There were no studies of the effect of SLIT on healthcare utilization.

Pulmonary Physiology

PEF. PEF was reported in 4 studies[79, 84, 86, 87] including a total of 281 patients. One study included only adults, two children, and one mixed age population. The risk of bias was low in 2 studies and medium in two. All studies compared SLIT with placebo. While none of the studies demonstrated statistically

significant improvement when compared to controls, 1 of the 3 studies showed minimal improvement in those treated with SLIT with PEF decreasing by 1.97 in the SLIT group compared to 1.12 in the control group after treatment. [84]

FEV_1. FEV_1 was the most commonly reported outcome, reported in nine studies. [74, 76, 77, 79, 82, 86-88] Five of these studies were in adults only,[74, 76, 77, 79, 82] and three in children,[86-88] and one in a mixed age population.[74, 84] The total number of patients in these studies was 1574 with mild to moderate asthma. Six studies were of HDM, one grass mix, one birch, and one timothy grass. When considering seasonal allergens, two pollen allergen studies found statistically significant improvement in FEV_1. One trial of grass mix SLIT versus control (treated with montelukast alone), at a dose of 5 drops of 10,000RU/ml 3 times a week for 5 years, reported an increase from an average of 78.5% to 96.2% of predicted FEV_1 in the SLIT group, compared to change in control group of 76.4% to 81.2% ($p<0.0001$).[82] The second study, of birch allergen, was performed with a dose pre/co-seasonal 1000AU tablets 5 days a week for 3 years, and reported that mean FEV_1 improved from 85.2 to 103.3 in the SLIT group, in comparison to 3 control groups treated with budesonide alone which improved from 88.3 to 90.3, 87.0 to 92.4, and 86.2 to 96.5 ($p <0.05$ for SLIT compared to any of the control groups).[76] Of the remaining 7 studies, three demonstrated a non-statistically significant improvement in those treated with SLIT. The risk of bias was medium in four studies, low in four, and high in one study. SLIT may improve FEV_1, based on evidence that is precise, direct, consistent, and with a medium overall risk of bias (low SOE).

FEV1/FVC. There were no studies of the effect of SLIT on FEV1/FVC.

FVC. One study reported on the effect of SLIT on FVC.[87] This is discussed in the pediatric section below.

Airway Hyperresponsiveness

Methacholine challenge. Three studies reported methacholine challenges results, with two birch studies in adults with mild asthma,[76, 82] and one HDM study in a mixed age population with severe asthma.[83] There were no studies of only children. The number of included patients totaled 173. Both birch studies demonstrated significant improvement in AHR after treatment with SLIT. The first birch study reported methacholine dose in micrograms causing a 20 percent fall in FEV1 from baseline (PD_{20}), with the change in dose in the SLIT group improving by 592.9 after treatment, compared to the control group which was treated with montelukast alone of 190.1 (P=0.001).[82] The second birch study reported methacholine dose in micrograms causing a 20 percent fall in FEV1 from baseline, with the SLIT group improving from 166.8 to 997.1 after treatment, compared to 3 control groups: budesonide 800 micrograms (from 226 to 520.0 µg of methacholine PD20), budesonide 1600 micrograms (from 199.8 to 644.9), budesonide 400 micrograms plus montelukast 165.7 to 728.7 (SLIT versus all treatment arms $P<0.05$). The HDM study reported increases in cumulative methacholine dose in micrograms causing a reduction of 20 percent of the baseline FEV1 for the SLIT group improving from 626.4 to 1277.7 after treatment (p=0.001), in comparison to 616.1 to 860.3 for the control group which was treated with non-specified pharmacotherapy (P=0.08); however, this study did not make a direct statistical comparison of SLIT to SCIT for the methacholine challenge outcome. The maintenance dosing utilized for the studies included: HDM 1000 AU 2 times a week for 1 year, birch 5 drops of 10,000AU/ml 3 times a week for 5 years, and birch 1000 AU 5 days a week pre/co-seasonal 5 days a week. Two small studies with medium to high risk of bias demonstrated statistically significant improvement compared to controls.

Allergen challenge. There were no studies of the effect of SLIT on allergen challenge.

Exercise challenge. There were no studies of the effect of SLIT on exercise challenge.

Compliance

Four HDM studies reported compliance in mild-moderately persistent asthmatics reported on compliance. Three adult studies, including 1022 patients, reported compliance outcomes.[74, 75, 77] Compliance in these trials ranged from 90 to 99 percent. One study reported compliance as mean compliance with study drug, the second study as the number of non-compliant patients, and the third by determining the number of unused SLIT packs. One study in children only, of 86 patients, reported "excellent compliance and no dropouts at six months".[88]

Immunological Outcomes

Skin testing. Three placebo controlled SLIT trials report allergen skin testing results for HDM.[77, 84, 89] Two studies using HDM SLIT tablets demonstrated statistically significant reduction in skin wheal diameter when comparing SLIT baseline and post-therapy values and mean differences between SLIT and placebo groups.[77, 84]

Immunoglobulin E. Six SLIT aqueous or tablets versus placebo RCTs reported HDM specific IgE levels.[77, 84-87, 89] Only one study reported a statistically significant effect: an increase in HDM specific IgE levels after SLIT tablets compared to placebo ($P<0.001$).[84]

Immunoglobulin G4. Four RCTs using SLIT reported HDM specific IgG4 levels.[73, 77, 84, 86] Three studies reported statistically significant increases in specific IgG4 levels after SLIT in comparison to placebo.[73, 77, 84, 86] One study comparing 2 doses of HDM SLIT tablets versus placebo along with inhaled corticosteroids in 834 HDM allergic asthmatics, measured IgG4 levels for both Der p1 and Der f. They report significant increases in both Der p1/Der f1 specific IgG4 at both doses when compared to placebo ($P<0.001$).[73] Two other studies also reported significant increases in specific IgG4 using aqueous and tablet forms of SLIT (respectively, $P<0.01$ and $P=0.026$).[84, 86]

Variation per Setting

Ten studies of SLIT did not specify setting,[74, 79-82, 84-88] four reported administration at home[75, 76, 78, 83] and two specify administration at the clinic.[73, 77] The body of evidence is insufficient to draw conclusions on any variation per setting.

Variation per Population

Adults

Asthma symptoms. When examining studies on adults, there was no variation compared to the full body of evidence in asthma symptoms. See description above.

Quality of life. When examining studies on adults, there was no variation compared to the full body of evidence in Quality of Life. See description above.

Medication use. When examining studies on adults, there was variation compared to the full body of evidence in the long term control medication use. The two studies performed in adults demonstrated significant decrease in the used of inhaled corticosteroids with treatment using a maintenance dose of 300 IR or 6 SQ-HDM.[74, 77] This was not demonstrated in the two other studies of children and mixed age population. No studies evaluated quick relief medications or systemic corticosteroids use in adults only.

Asthma exacerbations. When examining studies on adults, there was no variation compared to the full body of evidence in asthma exacerbations. See description above.

Healthcare utilization. There were no studies of the effect of SLIT on healthcare utilization in adults.

Pulmonary physiology. When examining studies on adults, there was no variation compared to the full body of evidence in the pulmonary physiology. Five studies including 1520 patients with mild to moderate asthma treated with HDM reported on pulmonary physiology.[74, 76, 77, 79, 82] Results in the section above.

Airway hyperresponsiveness. When examining studies on adults, there was no variation compared to the full body of evidence in airway hyperresponsiveness when using methacholine challenge. See description above.

Compliance. Three adult HDM studies reported compliance outcomes in a total of 1022 mild-moderately persistent asthmatics.[74, 75, 77] Compliance in these trials ranged from 90 to 99 percent. One study reported compliance as mean compliance with study drug, the second study as the number of non-compliant patients, and the third by determining the number of unused SLIT packs. Compliance was similar in the placebo arms.

Children

Three studies including 216 children reported on the efficacy of SLIT in children ages 5-12 years with asthma. All studies enrolled children with mild to moderate persistent asthma. All studies used HDM SLIT in children who were monosensitized to HDM, and compared SLIT to placebo.[86-88]

Asthma symptoms. There were no studies of the effect of SLIT on asthma symptom outcomes using ACT, ACQ or P-ACT scores in children.

Quality of life. There were no studies of the effect of SLIT on asthma quality of life using the AQLQ, Pediatric Asthma Specific Quality of Life, or school/ work absences in children.

Medication use. One trial of HDM SLIT versus placebo in 110 children with mild to moderate persistent asthma reported on the use of asthma specific medications after a 24 week intervention.[87] This study found no difference in the use of quick relief medication (Beta-agonists puffs per day) within or between groups. It also found no difference within or between groups for the use of long term control medications (inhaled corticosteroids- puffs per day) or in the use of systemic corticosteroids (tablets per day). Overall strength of evidence is insufficient, based on a single small RCT with medium risk of bias.

Asthma exacerbations. There were no studies of the effect of SLIT on asthma exacerbations in children.

Healthcare utilization. There were no studies of the effect of SLIT on healthcare utilization in children.

Pulmonary physiology

PEF. Two studies reported on PEF as an outcome in children. One included 20 patients and noted an improvement in evening but not morning PEF values compared to baseline in the SLIT arm.[86] The second study with 110 patients demonstrated that PEF did improve significantly at follow up compared to baseline in only the SLIT group.[87] Neither study noted a significant difference between arms.[86, 87]

FEV_1. Three studies reported FEV_1 values.[86-88] These studies included 216 children. All three studies noted a statistically significant improvement in FEV_1 in the SLIT arm but there was no statistically significant difference between arms.[86-88] The overall strength of evidence is low that SCIT improves FEV_1 in children based on three RCTs with medium risk of bias, with consistent but imprecise results.

FEV_1/FVC. There were no studies of FEV_1/FVC in children only.

FVC. One study reported FVC values and found that children in the SLIT arm had significant improvement at the end of treatment but there was no significant change in the placebo arm. There was however no significant difference between arms.[87]

Airway hyperresponsiveness. There were no studies of the effect of SLIT on airway responsiveness in children.

Compliance. One study reported that compliance was excellent after 6 months of treatment, no patient interrupted SLIT and no data was provided for control arm.[88]

Table 5- Summary of the Strength of Evidence for the Efficacy of Sublingual Immunotherapy

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	Strength of Evidence
Asthma Symptoms ACT	4 RCTs [73, 74, 76, 77] N=1510	Low	Consistent	Direct	Precise	Undetected	SLIT improves asthma symptoms	High
Quality of Life AQLQ	3 RCTs [73, 74, 77] N=1120	Low	Consistent	Direct	Precise	Undetected	SLIT improves asthma QOL	Moderate.
Medication Use Quick relief medication	4 RCTs [76, 81, 82, 87] N=349	Medium	Consistent	Direct	Imprecise	Undetected	SLIT may reduce the need of quick relief medication	Low
Medication Use Long term control medication	4 RCTs [87] N=1409	Medium	Consistent	Direct	Precise	Undetected	SLIT reduces the need of long term control medication	Moderate
Medication Use Systemic Corticosteroids use	1 RCT[87] N=110	Medium	NA	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	Strength of Evidence
Healthcare Utilization	No RCTs	NA	NA	NA	NA	Undetected	Unable to draw conclusions	Insufficient
Pulmonary Physiology FEV_1	9 RCTs[74, 76, 77, 79, 82, 84, 86-88] N=1574	Medium	Consistent	Direct	Precise	Undetected	SLIT may improve pulmonary function (FEV_1)	Low

Key Question 4. What is the evidence for the safety of sublingual immunotherapy (SLIT) in the treatment of asthma?

Key Points

- Local reactions to SLIT were frequent (some reactions occurring in up to 80% of patients in RCTs); however reactions also commonly occurred with placebo (risk differences ranged from -0.03 to 0.765).
- Systemic reactions to SLIT were frequent (some reactions occurring in up to 22% of patients in RCTs), with only few reports of anaphylaxis and no reports of deaths (risk differences ranged from -0.03 to 0.06).
- There was insufficient evidence to draw conclusions regarding effect of SLIT on anaphylaxis (no cases reported in RCTs, 3 case reports) or death (none reported).
- All 3 reports of anaphylaxis secondary to SLIT were in patients who received multiallergen therapy.

Overall Study Characteristics

Our search identified a total of 24 articles on 21 unique studies/populations reporting safety data. Of the included studies, 13 were randomized controlled trials (16 articles [73-79, 83, 84, 90-96]) while eight were either cohort, case-control, or case reports.[97-104]

Details on study, patient characteristics, and interventions are provided in Appendix G and components in the assessment of risk of bias are shown in Appendix I.

Summary and Description of Characteristics in RCTs

Sixteen RCTs enrolled adults, four enrolled mixed age populations[83, 84, 94, 95] and four enrolled children only.[86-88, 96] Half used GINA criteria to identify asthmatics,[73-76, 78, 90, 91, 94, 95] while the other half used a positive methacholine challenge, bronchodilator reversibility, or did not describe the methods used. Asthma severity ranged from mild to severe persistent, with two studies specifying the recruitment of poorly-controlled patients.[73, 76] Allergy was diagnosed in all studies using skin-prick testing. All but one study supplemented this criteria with specific IgE elevation.[83] Patients were monosensitized in six studies[76, 78, 79, 84, 94, 95] and polysensitized in three studies.[77, 93, 96] Four studies included both polysensitized and monosensitized patients,[73-75, 83] All studies examined single allergen therapy, with allergens including HDM, birch, and grass. Five studies compared different doses of SLIT and included a placebo arm,[73-75, 79, 90, 91, 94] while the remaining seven compared SLIT versus placebo, control, or

standard asthma pharmacotherapy.[76, 77, 83, 84, 92, 93, 95, 96] Studies variably reported on treatment for adverse events or discontinuation of SLIT therapy due to adverse events, and many did not report whether adverse events were considered drug-related. Four studies took place in a clinic setting,[73, 77, 92-94] four in the home,[75, 76, 78, 83] and the remainder did not specify setting. (Appendix G-Table 1A for patient characteristics and Table 3A for SLIT dosing characteristics.)

Adults. Eight studies included adults only,[73-77, 79, 90-93] and one reported results separately for adults. [94] Five used GINA criteria for asthma identification.[73-76, 90, 91, 94] Asthma severity ranged from mild to severe persistent, and two studies specified recruitment of poorly-controlled patients.[73, 76] Just under half of the adult studies contained polysensitized patients. HDM, birch, and grass allergens were represented. Five trials compared different doses of SLIT and included a placebo arm,[73-75, 79, 90, 91, 94] while the remaining studies compared a SLIT versus placebo, control, or standard asthma pharmacotherapy.[76-78, 93] Four studies took place in the clinic,[73, 77, 93, 94] three at home[75, 76, 78] and one did not specify setting.

Children. Four studies including 270 children reported safety data for the use of SLIT. All studies included patients with mild to moderate persistent asthma. Three studies including 216 patients compared HDM SLIT to placebo in patients who were monosensitized to HDM.[86-88] One study evaluated ultra-rush high dose birch pollen SLIT in patients with tree pollen allergy.[96]

Summary and Description of Characteristics in Non-RCTs

We included eight non-RCTs, of which four were case reports and included adults,[97-100] two enrolled mixed-age populations[101, 102] and two children only. [103, 104] Only one study described asthma diagnosis criteria, and it used pulmonary function tests.[104] Asthma severity ranged from mild intermittent to moderate persistent, and was not specified for four of the studies.[97, 98, 100, 104] Asthma control was also variably described. Seven studies used skin-prick testing for diagnosis, with four adding IgE criteria [98, 99, 101, 102] and one which did not specify atopic criteria.[100] Patients were monosensitized in two studies[103, 104 118] and polysensitized in three studies.[97-99] One study included both polysensitized and monosensitized patients,[102] one study did not clearly report sensitization status[101] and one study did not report allergen identified.[100] Three case reports examined administration of multiple allergen SLIT,[97, 98, 100] while the others examined single allergen therapy with HDM or grass. Studies variably reported on treatment for adverse events or discontinuation of SLIT therapy due to adverse events. Four studies took place at least partially in the home,[97, 100, 103, 104] the others in clinic or hospital. (See Appendix G-Table 1 Study characteristics, and Table 3 for SLIT dosing characteristics.)

Adults. All four non-RCTs of adults only were case reports.[97-100] Three included polysensitized patients.[97-99] and two of those were given multiple allergen SLIT[97, 98] Patients in one study in which allergic status was not specified also received multiple allergen.[100] Two studies occurred in the home,[97, 100] one in the clinic[98] and one was not specified[99] (Appendix G).

Children. Two studies reported safety data for the use of SLIT in children with asthma.[103, 104] Both studies were case reports and included monosensitized patients to HDM and received single allergen SLIT.

Hypersensitivity

No studies reported specifically on hypersensitivity reactions, however all local, systemic, anaphylactic, and some of the "other" reactions are considered hypersensitivity reactions.

Local Reactions

Summary and description of events in RCTs

Local events including pruritus/swelling of the mouth, tongue or lip, were reported in seven RCTs including roughly 2200 patients,[73, 74, 77-79, 84, 91, 94] with risk differences between SLIT therapy and placebo ranging from 0.1 to 0.765. Throat irritation was reported in five studies including roughly 1602 patients,[73, 74, 78, 79, 91, 94] with risk differences ranging from -0.03 to 0.09. Abdominal pain, nausea, vomiting, and other gastrointestinal complaints were reported in six studies including roughly 1800 patients,[73, 77, 79, 84, 93, 94] with risk differences ranging from -0.004 to 0.384. Also reported were local rashes in two studies with just over 700 patients.[77, 93] Frequency of local reactions was not usually dose-dependent. Participants in trials reporting local reactions had largely mild to moderate asthma, with one study not specifying severity.[73] Only one of the included studies took place in the home reporting risk difference between SLIT therapy and placebo of 0.063.[78] (Appendix G for further detail.)

Adults. Five of the seven RCTs reporting pruritus/swelling of the mouth, tongue or lip,[73, 74, 77, 79, 91, 94] four of the five studies reporting throat irritation,[73, 74, 79, 94] five of the six studies reporting abdominal pain, nausea, vomiting, and other gastrointestinal complaints,[73, 77, 79, 93, 94] and both of the studies reporting local rashes[77, 93] were either exclusively conducted in adults or reported results separately in an adult population. The risk difference in the adult population were therefore similar to those in the overall population. (Summary above.)

Children. One trial comparing birch SLIT versus placebo reported local reactions including application site itching and paresthesia. The number of reactions was not included.[96] Another study comparing HDM SLIT versus placebo in 110 patients reported local reactions (tongue disorder, vomiting, abdominal pain, and circumoral paresthesia) in 5 children (10 incidences) in the SLIT group.[87] One study found that there were no relevant local side effects in 86 children. [88] One study did not comment on local reactions. [86]

Summary and description of events in non-RCTs

Adults. Abdominal pain, nausea, and vomiting was noted in one case report of a polysensitized adult female receiving single allergen (HDM) therapy at home (Table 2e).[99] No other local reactions were documented in non-RCTs.

Children. No non-RCT studies with children only reported local reactions to SLIT.

Systemic Reactions

Summary and description of events in RCTs

Reported systemic events included lower respiratory symptoms in six RCTs including roughly 1840 patients,[91 73, 79, 84, 93, 94] with risk differences between SLIT and placebo ranging from -0.03 to 0.06. Mucosal irritation (other than mouth or gastrointestinal tract) was reported in five studies encompassing roughly 2200 patients,[73, 74, 77, 91, 93, 94] with risk differences of 0.025 to 0.035. Cutaneous systemic reactions were reported by one study (2 of 78 patients) and resolved without treatment.[76] This study was also the only study conducted in the home setting that reported systemic reactions. All participants in studies reporting systemic effects had mild to moderate asthma (one study did not specify asthma severity),[73] and incidence of systemic reactions was not strongly tied to higher dose. (Appendix G).

Adults. Four of six studies documenting lower respiratory symptoms,[91 73, 79, 93, 94] demonstrated an identical range of risk difference between SLIT and placebo to that described above for all studies.

Children. No RCTs of children only reported systemic reactions to SLIT. One study commented that there were no systemic reactions in 86 patients treated with HDM SLIT or placebo.[88]

Summary and description of events in non-RCTs

Lower respiratory symptoms were reported in three studies,[102-104] with asthma severity ranging from mild intermittent to moderate persistent. Two of the studies reported SLIT administered at least part of the time in the home. (See Appendix G – Table 2f for further detail.)

Adults. No non-RCTs with adults reported systemic reactions to SLIT.

Children. One case was reported of a 6-year-old male with persistent asthma and HDM allergy. Asthma symptoms were well controlled on daily fluticasone. PEF was 75% predicted and FEV_1 was 85% predicted and was reversible with bronchodilator. HDM SLIT was initiated (Dfar;D.pter. =50:50, 300 IR/ml). Following induction phase when he reached maintenance dosing (8 pumps) he developed wheezing within 2 minutes of his dose and symptoms persisted for 25 minutes and resolved with beta agonist (grade 2 reaction). He continued HDM SLIT at a reduced maintenance dose (4 pumps) and completed 3 years of therapy.[104]

Anaphylaxis

Summary and description of events in RCTs

No episodes of anaphylaxis were noted in five studies [73, 75, 84, 93, 96] including mono- and poly-sensitized patients with mild to severe persistent asthma, with SLIT administered in the clinic setting or at home. Four studies evaluated house HDM (dose ranged up to 12 SQ), and one evaluated birch (dose not available). [96] (See Appendix G for further detail.) Overall, there was insufficient SOE on the association of SLIT with anaphylaxis. The findings were consistent, but the risk of bias was medium. There were no events in the SLIT and control arms within 1292 patients treated.

Adults. Three studies in adults[73, 75, 93] specifically reported no episodes of anaphylaxis with HDM SLIT administered in the clinic setting or the home. Dose ranged up to 12 SQ, and included patients were either mono- or poly-sensitized patients with mild to severe persistent asthma.

Children. No RCT studies with children only reported anaphylactic reactions to SLIT.

Summary and description of events in non-RCTs

Three case reports, all in adults, reported anaphylactic reactions to SLIT therapy. The first was a 16 year-old female who received multiallergen SLIT and developed anaphylactic shock.[100] The second was a polysensitized 25 year-old female who received multiallergen SLIT who developed flushing, hoarseness, dyspnea, dizziness, and mild hypotension.[98] The last was a polysensitized, 31 year old female who received multiallergen SLIT and developed anaphylaxis.[97] Asthma severity and control were not identified in any of the cases. For one case SLIT was discontinued, for another it was maintained at a low dose, and for a third the ultimate therapy decision was not noted. All three received aqueous SLIT, two in a home setting and one in a clinic setting. Following WHO criteria for assessing case reports, we determined that it was certain that SLIT caused these reactions of anaphylaxis

(causality) in two cases,[97, 100] and likely caused reaction in one case,[98] with the main difference being that this reaction was not time related. (See Appendix G for further detail.)

Death

No deaths were reported in any of the studies evaluated.

Other

Please see Appendix G for reactions that were not otherwise classified. These included studies for which no serious reactions were reported, specific reactions were not specified, or reactions could not be categorized and it was unclear that the reaction was mechanistically related to SLIT therapy.

Conclusions

Most reported reactions were local with fewer systemic reactions noted. Occurrence did not differ systematically by setting of administration: home versus clinic versus other. Most studies looked at single allergen therapy with HDM extract, which was generally well-tolerated. Dose of SLIT did not demonstrate a clear association with risk of adverse events in all studies, though a subgroup of individual studies did report an association. One study comparing adult and child populations noted that adverse events tended to occur at lower doses in children than with adults.[94] No episodes of anaphylaxis were reported in RCTs, and 3 case reports of anaphylaxis were found among those who were polysensitized and/or treated with multiple allergen extracts. RCTs did not consistently report medication use or SLIT discontinuation in response to adverse events, though several studies did one or both. Of the three case reports of anaphylaxis, only one required a definite discontinuation of therapy (one followed a modified protocol of dosing and the other was not reported). No reports of death secondary to SLIT were found.

Table 6- Summary of the Strength of Evidence for the Safety of Sublingual Immunotherapy

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	Strength of Evidence
Anaphylaxis	5 RCTs [73, 75, 84, 93, 96] N=1292 No cases No Non-RCTs	Medium	Inconsistent	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient
	3 case reports[97, 98, 100]	2 Certain 1 Likely (Likelihood of causality)					Unable to draw conclusions	
Death	No studies reported on death	NA	NA	NA	NA	Undetected	Unable to draw conclusions	Insufficient

Subcutaneous Versus Sublingual Immunotherapy

Key Points

- There is insufficient evidence to assess the relative efficacy of SCIT versus SLIT.
- There is insufficient evidence to assess the relative safety of SCIT versus SLIT.

Overall Study Characteristics

We included six studies published between 1989 and 2016 that reported on the efficacy and safety of SCIT versus SLIT.[105-111] The studies included 267 patients, all studies used skin prick test for allergy diagnosis, included patients monosensitized and used HDM as allergen, except for one study that included polysensitized patients and used multiple allergens.[111]

Details on study, patient characteristics, and interventions are provided in Appendix H and components in the assessment of risk of bias are shown in Appendix I.

Asthma Symptoms

One study of SCIT versus SLIT aqueous HDM therapy reported asthma symptoms using the ACT.[106] The study included 90 adult and pediatric patients. Asthma severity was not specified. The study reported that both the SCIT and SLIT arms had statistically significant improvement when comparing pre and post treatment scores, and when compared to treatment with a combination inhaled steroid and short acting bronchodilator (pre/post improvement in scores: SCIT 5.91, SLIT 4.29, control 4.27). However, the article did not report a direct comparison of ACT score for the SCIT to SLIT treatment groups.

The strength of evidence is insufficient to draw conclusions on the efficacy of SLIT versus SCIT on asthma symptoms.

Quality of Life

No SCIT versus SLIT that met inclusion criteria for this review reported on quality of life.

Medication Use

No SCIT versus SLIT studies that met inclusion criteria for this review reported on medication use.

Asthma Exacerbations

No SCIT versus SLIT studies that met inclusion criteria for this review reported on asthma exacerbations.

Healthcare Utilization

No SCIT versus SLIT studies that met inclusion criteria for this review reported on healthcare utilization.

Pulmonary Physiology

One RCT of SCIT versus SLIT for HDM in comparison to medication alone reported pulmonary physiology outcomes in 90 mixed aged patients in the form of PEF and FEV_1.[106] Asthma severity was not specified. The study reported that both the SLIT and SCIT arms had statistically significant improvement when comparing pre and post treatment PEF and FEV_1, and when compared to treatment with a combination inhaled steroid and short acting bronchodilator. However the article did not report a direct comparison of the SCIT to SLIT treatment groups for these pulmonary physiology measures. The strength of evidence is insufficient to draw conclusions on the efficacy of SLIT or SCIT of pulmonary function.

Airway Hyperresponsiveness

Methacholine Challenge

One adult HDM study reported methacholine challenge results in 90 adults patients treated with SCIT, SLIT aqueous immunotherapy, or placebo/pharmacotherapy.[105, 108] The study did not specify asthma severity. The study reported non-statistically significant changes in AHR after treatment with one year of treatment in any of the groups. The publications did not report a direct comparison of results of those treated with SCIT with those treated with SLIT, nor was the specific data on the methacholine challenge values reported.

Allergen Challenge

One mixed age HDM study of patients with mild persistent asthma reported bronchial provocation results with HDM after one year of treatment with SCIT (0.2-0.8 ml of 5000 TU/ml monthly), SLIT (28 drops of 100 TU/ml 3 times a week), or placebo. The total number of patients in this study was 32. There was a statistically significant improvement pre versus post treatment in the SCIT group only (P=0.003). However, when comparing SCIT to SLIT patients, there was no statistically significant difference in HDM bronchial provocation.[107]

Exercise Challenge

No SCIT versus SLIT studies that met inclusion criteria for this review reported this outcome.

Immunological Outcomes

Four studies compared HDM specific IgE levels between patients receiving SCIT versus SLIT.[105, 106, 108, 110] Two studies report individual statistically significant decreases in HDM specific IgE at baseline and after SCIT or SLIT compared to placebo.[106, 110]

Two RCTs reported HDM specific IgG4 levels over 1 year comparing SCIT, SLIT, and placebo.[107, 108] One trial found that only SCIT was associated with an increase in HDM specific IgG4 compared to either SLIT or SCIT.[107] Another RCT compared 4 groups: SCIT, SLIT, SCIT in addition to SLIT, and pharmacotherapy and reported HDM specific IgG4 increases in only the SCIT and SCIT+SLIT groups when compared to pharmacotherapy alone.[108]

Safety SCIT vs SLIT

Hypersensitivity

No studies reported specifically on hypersensitivity reactions, however all local, systemic, anaphylactic, and some of the "other" reactions are considered hypersensitivity reactions.

Local Reactions

Three of the five RCTs reported local reactions.[105, 106, 110] In two studies the incidence of reactions at the site of AIT application were comparable for SCIT and SLIT (13 vs 10 percent)[105] and one out 30 patients presenting grade 2 events in each arm.[106] Whereas incidence was higher for SLIT in one study: oral itching was reported in only one of 16 patients in the SLIT arm,[110] and higher for SCIT in a second study: 10 out 27 patients receiving SCIT presented Grade 1 events compared to 3 out of 30 receiving SLIT. (Appendix H)

Systemic Reactions

Four of five RCTs reported systemic events.[105, 106, 108, 110] Respiratory symptoms were reported only for SCIT [105, 108, 110] with an incidence ranging from 6 to 18 percent (one or two patients). Gastrointestinal events (mild nausea) were reported only for one patient receiving SLIT.[105] One study reported events as unspecified systemic reactions; events were higher for SCIT than SLIT (two patients versus one out of 30 in each arm).[106](Appendix H)

Anaphylaxis

One study reported a case of anaphylactic reaction to SCIT therapy. One out 16 patients receiving SCIT presented flushing, wheezing and dyspnea requiring adrenaline and required treatment discontinuation. All patients receiving SLIT (n=16) and pharmacotherapy (n=16), were able to complete the study.[110]

Safety in Non RCTs

We included one case series that compared SCIT versus SLIT.[111] It reports on two cases of adolescents (14 and 13 year old) receiving SCIT, who presented painful local reactions at the site of injection, significant enough to discontinue therapy but were started on SLIT looking for a safer safety profile. However, none of these patients tolerated treatment, they both developed respiratory reactions and asthma worsening. They both required treatment discontinuation. (Appendix H)

Death

No deaths were reported in any of the studies evaluated.

Table 7- Summary of the Strength of Evidence for SCIT versus SLIT

Outcome	N of studies (n of patients)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Conclusion	Strength of Evidence
Asthma Symptoms ACT	1 RCT[106] N=90	Medium	NA	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient
Quality of Life AQLQ	No studies	NA	NA	NA	NA	Undetected	Unable to draw conclusions	Insufficient
Medication Use	No studies	NA	NA	NA	NA	Undetected	Unable to draw conclusions	Insufficient
Healthcare Utilization	No studies	NA	NA	NA	NA	Undetected	Unable to draw conclusions	Insufficient
Pulmonary Physiology FEV1	1 RCT[106] N=90	Medium	NA	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient
Anaphylaxis	1 RCT[110] N=16	Low	NA	Direct	Imprecise	Undetected	Unable to draw conclusions	Insufficient
Death	No studies	NA	NA	NA	NA	Undetected	Unable to draw conclusions	Insufficient

FEV1 – Forced Expiratory volume

Discussion

We identified a total of 71 RCTs and 24 non-RCTs addressing the efficacy and safety of SCIT and SLIT. Thirty-one RCTs assessed the efficacy of SCIT. We found moderate strength of evidence that SCIT reduces the need for long term control medications. We also found that SCIT may improve quality of life, reduce the use of quick relief medication, reduce the need for systemic corticosteroids, and improve FEV_1 (low SOE). We found insufficient evidence to make conclusions about the effect of SCIT on asthma symptoms, and for healthcare utilization.

Local reactions to SCIT are frequent, occurring in up to a third of patients; however, reactions also commonly occur with placebo injections, and infrequently require a change in the SCIT dosing. Systemic reactions to SCIT are relatively common, and were reported in up to 33 percent of adult patients. A small proportion of these reactions were consistent with anaphylaxis requiring treatment with injectable epinephrine (of the total 180 systemic reactions reported in RCTs, we determined that six cases were consistent with of anaphylaxis and there was one case reported from the 165 non-RCTs). Patients had mild to moderate asthma in most studies. However, in many studies the diagnosis of asthma was not specified, and in the majority the status of asthma control prior to treatment with SCIT was not specified. Several studies described an accelerated SCIT protocol, and it did not appear that the risk of systemic reactions was higher with such protocols. SCIT in patients with asthma generally has a favorable safety profile; however systemic reactions do occur, some of which require treatment with injectable epinephrine, and careful monitoring for such reactions is appropriate.

The efficacy of SLIT for asthma was assessed in 16 RCTs. We found high strength of evidence that SLIT reduces asthma symptom outcomes. There was moderate grade evidence for the benefit of SLIT in asthma specific quality of life and in reducing the use of long term control medications (inhaled corticosteroids). SLIT may also reduce the use of quick relief medication (low SOE).

We found that local adverse events were common with use of SLIT, occurring in up to 40 percent of patients, but that systemic and life threatening events were not commonly reported. It is important to note that all reported anaphylaxis events (3 case reports) occurred in patients receiving multiallergen therapy, perhaps signaling that this form of therapy poses higher risk for systemic adverse effects. Furthermore, the rate of adverse events did not show a consistent relationship with SLIT dose.

Our findings are similar to those of the prior JHU EPC evidence report and other prior systematic reviews. The Cochrane review of SCIT concluded that there was a significant reduction in asthma symptoms and asthma medications, as well as improvement in allergen specific bronchial hyper-reactivity.[8] The prior evidence report similarly concluded that there was high strength of evidence that SCIT reduces asthma symptoms and medication use.[10] Both of these reviews noted the significant heterogeneity between the studies, as we found. In contrast, we could not draw conclusions about the effect of SCIT on asthma symptoms as we limited our review to studies that used validated tools to measure asthma symptoms and identified none. A 2015 Cochrane review found there was low quality evidence supporting the use of SLIT in changing inhaled corticosteroid use, and very low quality evidence regarding bronchial provocation.[9] This Cochrane review further noted that the largely unvalidated asthma symptom scores, medications scores, and the available data for quality of life precluded meaningful synthesis of these outcomes. Our prior evidence report examined SLIT in aqueous form only, and concluded that SLIT reduced asthma symptoms.[10] This review expanded our scope to consider SLIT in tablet form, and came to similar conclusions.

Limitations

We found considerable heterogeneity in the outcomes reported, and in the measurement of outcomes, that precluded quantitative pooling of the data. Many studies did not report relevant statistical information on continuous variables (such as confidence interval, standard deviation, and standard error)

and some studies did not report results between arms, also limiting our ability to synthesize the evidence.

It was a challenge to align some study findings with the age categories defined in asthma guidelines. National asthma guidelines recommend distinct treatment for children ages 5-11 years and consider treatments for children ages 12 and older to be the same as for adults. When we evaluated studies that included children and youth (i.e., less than 18 years) we found very few studies had set enrollment criteria to restrict populations that would fit neatly into either of the groups defined by the guidelines. Furthermore, data were not reported in the studies to allow abstraction of subgroups that fit distinctly into these categories. Thus, a study that enrolled, for example, patients between the ages of 5 to 15 years s would have findings relevant to both age groups (5-11 and 12+), but for the purposes of this review, they were reported as mixed age groups. The result is that there was some information that could inform the overall question of immunotherapy efficacy that could not be used in subgroup analyses of children only or adults only.

We found extreme variability in the dosing and treatment schedules from study to study. The doses were reported in varying units (BU, IR, SQ-U, micrograms, BAU, STU, etc.). Some studies used conventional schedules, some used rush or ultra rush schedules. These variations made it very hard to compare outcomes across studies. In several studies, major allergen content was not reported and the study length varied from weeks to months.

There was much variability across studies in methods used for asthma diagnosis, as well as grading of asthma severity and control. Also, some studies did not provide information about baseline asthma severity or control. These issues may affect the generalizability of the findings to certain patients with asthma, and limited with our ability to determine whether asthma health status at the beginning of treatment affects the observed outcomes.

Unfortunately, there were some studies of SLIT and SCIT that could not be included in the analysis, either because validated measures of outcomes were not employed (e.g., use of a non-standardized "symptom score"), or because patients without asthma were also included in the study, but results were not presented separately for those with asthma. For example, some studies enrolled patients with allergic rhinitis and/or asthma which did not allow us to assess the impact of IT on asthma.

Only a small number of articles described some of the systemic reactions as "anaphylactic" reactions. However, upon review of the systemic reactions described, several of these reactions would be consistent with anaphylaxis, based on NIAID/FAAN criteria for diagnosis of anaphylaxis.[112]

Applicability

The results of this study are applicable to patients with inhalant allergy (as confirmed by skin or allergen specific in vitro testing) and asthma. Most studies were performed in adults or mixed aged populations, with only 11 studies of children. Almost all the trials utilized a single allergen for immunotherapy, therefore no comment can be made on multi allergen SCIT or SLIT. These studies were done almost exclusively in patients with mild to moderate persistent asthma, with a paucity of studies in those with severe persistent asthma. The dose and duration of treatment varied considerably in these studies. The studies were most numerous with HDM allergen; the number of studies of other allergens that met inclusion criteria for this review were limited.

Future Research Needs

We were limited in our ability to synthesize results due to lack of studies for specific populations, interventions and outcomes, substantial heterogeneity, and limited reporting. We detail below specific areas for future research.

Population.

- The overwhelming majority of studies that met inclusion criteria for this review included patients with mild-moderate asthma; there is a need to investigate the safety and efficacy of immunotherapy in patients with severe asthma.
- Not all studies provided information about asthma severity or control of study patients. Because severity and control are potentially important modifiers of treatment effect, studies are needed that clearly report the severity and control of enrolled patients.
- There were few studies conducted in children only, and few studies of all ages that reported outcomes for children separately. To inform asthma treatment guidelines, investigators should consider including only ages 5-11 years in studies, or if a broader age is studied, to report findings separately for those aged 5-11 years and those older..

Intervention and Comparison.

- There is a specific need for studies investigating the efficacy and safety of multiple allergen regimens for SCIT or SLIT. Multi-allergen treatment is frequently used in the US, but most of the studies include single allergen regimens. There is increasing discussion in the scientific community on the clinical use and efficacy of single allergen versus multiple allergen therapy, and there is a lack of studies which compare these head-to-head.
- There are few studies that compare SCIT to SLIT head to head.
- Immunotherapy dosing quantity, frequency, and formulation varied substantially and details were often lacking. Standardized methods and reporting of therapy would be helpful.
- Most studies we identified were of HDM allergen, and so additional studies of the efficacy of SCIT or SLIT treatment with other allergens would be useful.

Outcomes.

- For both SCIT and SLIT, studies are needed that address healthcare utilization.
- Many studies used non-validated scoring of outcomes. For instance, we found no trials of SCIT that assessed asthma symptoms using a validated tool. Future studies would benefit from standardized methods and validated instruments to report outcomes such as asthma symptoms, and adverse events.

Conclusion

SCIT reduces the need for long term control medication, and may improve asthma specific quality of life, use of quick relief medications, systemic corticosteroids use, and FEV1. SLIT improves asthma symptoms, reduces long term control medication use, improves disease specific quality of life, and may reduce the need for quick relief medication and improve FEV1. Local and systemic reactions to SCIT and SLIT are common but infrequently required changes in treatment. Life threatening events (such as anaphylaxis) are reported rarely. There is insufficient evidence on the comparative effectiveness of SCIT versus SLIT, or for differential effects by patient age, type of allergen, or setting .

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